Clinical trial results:
A Phase III, Multicenter, Randomized, Placebo-Controlled, Double-Blind Study of Atezolizumab (AntiPD-L1 Antibody) as Adjuvant Therapy in Patients With Renal Cell Carcinoma at High Risk of Developing Metastasis Following Nephrectomy

Summary

EudraCT number	2016-001881-27
Trial protocol	AT NL DE GB DK CZ BE PL ES IE FR IT
Global end of trial date	08 December 2022

Results information

Result version number	v3 (current)
This version publication date	30 July 2023
First version publication date	04 May 2023
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	WO39210

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03024996
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 December 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 December 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to evaluate the efficacy and safety of atezolizumab versus placebo in participants with renal cell carcinoma (RCC) who were at high risk of disease recurrence following resection.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 January 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 8
Country: Number of subjects enrolled	Australia: 14
Country: Number of subjects enrolled	Austria: 8
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Brazil: 36
Country: Number of subjects enrolled	Canada: 43
Country: Number of subjects enrolled	Chile: 13
Country: Number of subjects enrolled	China: 5
Country: Number of subjects enrolled	Czechia: 11
Country: Number of subjects enrolled	Denmark: 30
Country: Number of subjects enrolled	France: 22
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Ireland: 13
Country: Number of subjects enrolled	Israel: 11
Country: Number of subjects enrolled	Italy: 53
Country: Number of subjects enrolled	Japan: 39
Country: Number of subjects enrolled	Korea, Republic of: 17
Country: Number of subjects enrolled	Netherlands: 13
Country: Number of subjects enrolled	Poland: 23
Country: Number of subjects enrolled	Russian Federation: 44
Country: Number of subjects enrolled	Serbia: 8

Country: Number of subjects enrolled	Spain: 36
Country: Number of subjects enrolled	Taiwan: 16
Country: Number of subjects enrolled	Thailand: 4
Country: Number of subjects enrolled	Turkey: 8
Country: Number of subjects enrolled	Ukraine: 30
Country: Number of subjects enrolled	United Kingdom: 16
Country: Number of subjects enrolled	United States: 239
Worldwide total number of subjects	778
EEA total number of subjects	227

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)	496
From 65 to 84 years	282
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

5 participants were randomized but did not receive any treatment.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Atezolizumab

Arm description:

Participants received atezolizumab 1200 milligrams (mg) intravenous (IV) infusion every 3 weeks (q3w) for 16 cycles (each cycle=21 days) or 1 year (whichever occurred first).

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

Dosage and administration details:

Participants received atezolizumab 1200 mg administered via IV q3w for 16 cycles or 1 year (whichever occurred first).

Arm title	Placebo

Arm description:

Participants received placebo matching to atezolizumab q3w for 16 cycles (each cycle=21 days) or 1 year (whichever occurred first)

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

Dosage and administration details:

Participants received a placebo administered via IV q3w for 16 cycles or 1 year (whichever occurred first).

Number of subjects in period 1	Atezolizumab	Placebo
Started	390	388
Completed	0	0
Not completed	390	388
Consent withdrawn by subject	21	36
Physician decision	-	1
Death	57	55
Not specified	3	3
Disease relapse	1	-
Study terminated by sponsor	303	283
Lost to follow-up	5	10

Baseline characteristics

Reporting groups	
Reporting group title	Atezolizumab
Reporting group description:	
Participants received atezolizumab 1200 milligrams (mg) intravenous (IV) infusion every 3 weeks (q3w) for 16 cycles (each cycle=21 days) or 1 year (whichever occurred first).	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo matching to atezolizumab q3w for 16 cycles (each cycle=21 days) or 1 year (whichever occurred first)	

Reporting group values	Atezolizumab	Placebo	Total
Number of subjects	390	388	778
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)	248	248	496
From 65-84 years	142	140	282
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	59.7	59.6	
standard deviation	± 11.3	± 10.7	-
Gender Categorical Units: Participants			
Female	103	110	213
Male	287	278	565
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	41	38	79
Not Hispanic or Latino	334	327	661
Unknown or Not Reported	15	23	38
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	1	2
Asian	43	51	94
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	8	9	17
White	324	304	628
More than one race	0	1	1
Unknown or Not Reported	14	22	36

End points

End points reporting groups

Reporting group title	Atezolizumab
Reporting group description:	
Participants received atezolizumab 1200 milligrams (mg) intravenous (IV) infusion every 3 weeks (q3w) for 16 cycles (each cycle=21 days) or 1 year (whichever occurred first).	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo matching to atezolizumab q3w for 16 cycles (each cycle=21 days) or 1 year (whichever occurred first)	

Primary: Investigator-assessed Disease-Free Survival (DFS)

End point title	Investigator-assessed Disease-Free Survival (DFS)
End point description:	
Investigator-assessed DFS, defined as the time from randomization to death from any cause or the first documented recurrence assessed by investigator, whichever occurred first. Recurrence was defined as any of the following: Local recurrence of renal cell carcinoma (RCC), new primary RCC, or distant metastasis of RCC. Investigator-assessed DFS was analyzed similarly to the analysis of IRF-assessed DFS. The Intent-to-Treat (ITT) population was defined as all randomized participants regardless of whether the assigned study treatment was received. 9999999=small number of events to calculate the upper CI limit	
End point type	Primary
End point timeframe:	
From baseline up to first occurence of event by investigator assessment (up to approximately 64 months)	

End point values	Atezolizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	390	388		
Units: Months				
median (confidence interval 95%)	57.2 (44.6 to 9999999)	49.5 (47.4 to 9999999)		

Statistical analyses

Statistical analysis title	Investigator-Assessed DFS
Comparison groups	Atezolizumab v Placebo
Number of subjects included in analysis	778
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.495
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.15

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from randomization to death from any cause. The ITT population was defined as all randomized participants regardless of whether the assigned study treatment was received. 9999999=wasn't estimable due to small or no number of events.

End point type	Secondary

End point timeframe:

From baseline up to death due to any cause (up to approximately 64 months)

End point values	Atezolizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	390	388		
Units: Months				
median (confidence interval 95%)	9999999 (59.8 to 9999999)	9999999 (9999999 to 9999999)		

Statistical analyses

Statistical analysis title	OS
Comparison groups	Atezolizumab v Placebo
Number of subjects included in analysis	778
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8868
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.42

Secondary: Investigator-assessed DFS in Participants With Tumor-Infiltrating

Immune Cell (IC) 1/2/3

End point title	Investigator-assessed DFS in Participants With Tumor-Infiltrating Immune Cell (IC) 1/2/3

End point description:

Investigator assessed DFS for participants with PD-L1 expression of IC1/2/3 vs IC0, defined as the time from randomization to death from any cause or the first documented recurrence assessed by investigator, whichever occurred first. Investigator-assessed DFS was analyzed similarly to the analysis of IRF-assessed DFS. PD-L1 IC0 was defined as <1% and IC1/2/3 was defined as >=1% of tumor-infiltrating IC expressing PD-L1 as assessed by immunohistochemistry using SP142 assay. Recurrence was defined as any of the following: Local recurrence of renal cell carcinoma (RCC), new primary RCC, or distant metastasis of RCC. The ITT population was defined as all randomized participants regardless of whether the assigned study treatment was received. 9999999=small number of events to calculate the upper CI limit

End point type	Secondary

End point timeframe:

From baseline until first occurrence of DFS event (up to approximately 64 months)

End point values	Atezolizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	390	388		
Units: Months				
median (confidence interval 95%)	57.2 (44.6 to 9999999)	47.9 (38.6 to 9999999)		

Statistical analyses

Statistical analysis title	Investigator-assessed DFS

Statistical analysis description:

Participants With Tumor-Infiltrating IC 1/2/3

Comparison groups	Atezolizumab v Placebo
Number of subjects included in analysis	778
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.201
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	1.1

Secondary: IRF-assessed Event-free Survival (EFS)

End point title	IRF-assessed Event-free Survival (EFS)

End point description:

IRF-assessed EFS was defined as the time from randomization to death from any cause, or the first documented recurrence in participants without baseline disease by IRF or the first documented disease progression in participants identified as having baseline disease by IRF, whichever occurred first. Disease progression was defined as either unequivocal progression of baseline disease or new unequivocal lesions. The ITT population was defined as all randomized participants regardless of whether the assigned study treatment was received. 9999999=wasn't estimable due to small number of events.

End point type	Secondary

End point timeframe:

From baseline until first documented recurrence event (up to approximately 64 months)

End point values	Atezolizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	390	388		
Units: Months				
median (confidence interval 95%)	9999999 (54.1 to 9999999)	9999999 (45.4 to 9999999)		

Statistical analyses

Statistical analysis title	IRF-assessed EFS
Comparison groups	Atezolizumab v Placebo
Number of subjects included in analysis	778
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1396
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.06

Secondary: Independent Review Facility (IRF)-assessed DFS

End point title	Independent Review Facility (IRF)-assessed DFS

End point description:

IRF-assessed DFS was defined as the time from randomization to death from any cause or the first documented recurrence assessed by IRF, whichever occurred first. The ITT population was defined as all randomized participants regardless of whether the assigned study treatment was received. 9999999=wasn't estimable due to small number of events.

End point type	Secondary

End point timeframe:

From baseline until first documented recurrence event (up to approximately 64 months)

End point values	Atezolizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	390	388		
Units: Months				
median (confidence interval 95%)	9999999 (54.1 to 9999999)	9999999 (49.4 to 9999999)		

Statistical analyses

Statistical analysis title	IRF-assessed DFS
Comparison groups	Atezolizumab v Placebo
Number of subjects included in analysis	778
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2811
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.12

Secondary: IRF-assessed DFS in Participants With Tumor-Infiltrating IC 1/2/3

End point title	IRF-assessed DFS in Participants With Tumor-Infiltrating IC 1/2/3

End point description:

IRF-assessed DFS was defined as the time from randomization to death from any cause or the first documented recurrence assessed by IRF, whichever occurred first. PD-L1 IC0 was defined as <1% and IC1/2/3 was defined as >=1% of tumor-infiltrating IC expressing PD-L1 as assessed by immunohistochemistry using SP142 assay. The ITT population was defined as all randomized participants regardless of whether the assigned study treatment was received. 9999999=wasn't estimable due to small or no number of events.

End point type	Secondary

End point timeframe:

From baseline until first occurrence of DFS event (up to approximately 64 months)

End point values	Atezolizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	232	235		
Units: Months				
median (confidence interval 95%)	9999999 (9999999 to 9999999)	9999999 (41.4 to 9999999)		

Statistical analyses

Statistical analysis title	IRF-assessed DFS (Tumor-Infiltrating IC 1/2/3)
Comparison groups	Atezolizumab v Placebo
Number of subjects included in analysis	467
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0735
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.03

Secondary: Distant Metastasis-Free Survival

End point title	Distant Metastasis-Free Survival

End point description:

Distant metastasis-free survival, defined as the time from randomization to death from any cause or the date of diagnosis of distant (i.e., non-locoregional) metastases assessed by the investigator, whichever occurred first. The ITT population was defined as all randomized participants regardless of whether the assigned study treatment was received. 9999999=wasn't estimable due to small number of events.

End point type	Secondary

End point timeframe:

From baseline up to date of diagnosis of distant metastases or death due to any cause (up to approximately 64 months)

End point values	Atezolizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	390	388		
Units: Months				
median (confidence interval 95%)	9999999 (48.4 to 9999999)	52.9 (47.9 to 9999999)		

Statistical analyses

Statistical analysis title	Distant Metastasis-Free Survival
Comparison groups	Atezolizumab v Placebo
Number of subjects included in analysis	778
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5111
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.16

Secondary: Disease-Specific Survival

End point title	Disease-Specific Survival

End point description:

Disease-specific survival was defined as the time from randomization to death from renal cell carcinoma (RCC). The ITT population was defined as all randomized participants regardless of whether the assigned study treatment was received. 9999999=wasn't estimable due to no number of events.

End point type	Secondary

End point timeframe:

From baseline up to death due to RCC (up to approximately 64 months)

End point values	Atezolizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	390	388		
Units: Months				
median (confidence interval 95%)	9999999 (9999999 to 9999999)	9999999 (9999999 to 9999999)		

Statistical analyses

Statistical analysis title	Disease-specific survival
Comparison groups	Atezolizumab v Placebo
Number of subjects included in analysis	778
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4762
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.33

Secondary: Percentage of Participants Who Are Alive and IRF-assessed Recurrence Free at Year 1, 2, and 3

End point title	Percentage of Participants Who Are Alive and IRF-assessed Recurrence Free at Year 1, 2, and 3

End point description:

IRF-assessed DFS was defined as the percentage of participants being alive and free of recurrence assessed by IRF at Year 1, 2, and 3 after randomization. The ITT population was defined as all randomized participants regardless of whether the assigned study treatment was received.

End point type	Secondary

End point timeframe:

Up to 3 years

End point values	Atezolizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	390	388		
Units: Percentage of Participants				
number (not applicable)				
Year 1	81.01	76.42		
Year 2	70.40	68.22		
Year 3	65.04	62.71		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Are Alive and Investigator-assessed Recurrence Free at Year 1, 2, and 3

End point title	Percentage of Participants Who Are Alive and Investigator-assessed Recurrence Free at Year 1, 2, and 3

End point description:

Investigator-assessed DFS rate was defined as the percentage of participants being alive and free of recurrence assessed by investigator at Year 1, 2, and 3 after randomization. The ITT population was defined as all randomized participants regardless of whether the assigned study treatment was received.

End point type	Secondary

End point timeframe:

Up to 3 years

End point values	Atezolizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	390	388		
Units: Percentage of Participants				
number (not applicable)				
Year 1 (n=288, 275)	77.41	74.12		
Year 2 (n=244, 232)	67.32	65.01		
Year 3 (n=194, 187)	59.43	59.00		

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:

An adverse event (AE) was defined as any untoward medical occurrence in a 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 pharmaceutical product whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as a AEs. The safety population included all randomized participants who received any amount of study treatment, regardless of whether a full or partial dose was received.

End point type	Secondary

End point timeframe:

From baseline up to death due to any cause (up to approximately 71 months)

End point values	Atezolizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	390	383		
Units: Percentage of Participants				
number (not applicable)	95.6	89.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Serum Concentration (Cmax) of Atezolizumab

End point title	Maximum Serum Concentration (Cmax) of Atezolizumab[1]

End point description:

The pharmacokinetic (PK) population included all randomized participants who received any any dose of study treatment and who had at least one measurable post-baseline PK sample available.

End point type	Secondary

End point timeframe:

Predose (Hour[hr]0), 0.5 hr after end of infusion (infusion duration=1 hr) on Cycle 1 Day 1; predose (hr 0) on Day 1 of Cycles 2, 3, 4, 8; at treatment discontinuation (up to 1 year); 90-120 days after last dose (last dose = up to 1 year) (Cycle=21 days)

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics for atezolizumab were determined prior to this study. There are no statistics from this study.

End point values	Atezolizumab			
Subject group type	Reporting group			
Number of subjects analysed	369			
Units: Micrograms per milliliter (ug/mL)				
arithmetic mean (standard deviation)	399 (± 138)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Anti-Drug Antibodies (ADA) to Atezolizumab

End point title	Percentage of Participants With Anti-Drug Antibodies (ADA) to Atezolizumab[2]

End point description:

The immunogenicity analysis population will consist of all participants with at least one ADA assessment for atezolizumab. The post-baseline ADA evaluable population included all participants who received at least one dose of atezolizumab and with at least one post-dose ADA assessment.

End point type	Secondary

End point timeframe:

Predose (hr 0) on Day 1 of Cycles 1, 2, 3, 4, 8; at treatment discontinuation (up to 1 year); 90-120 days after last dose (last dose = up to 1 year) (Cycle=21 days)

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There are no statistics from this study.

End point values	Atezolizumab			
Subject group type	Reporting group			
Number of subjects analysed	390			
Units: Percentage of Participants				
number (not applicable)				
Baseline	1.8			

Treatment Emergent ADAs	26.4			

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Serum Concentration (Cmin) of Atezolizumab

End point title	Minimum Serum Concentration (Cmin) of Atezolizumab[3]

End point description:

The PK population included all randomized participants who received any any dose of study treatment and who had at least one measurable post-baseline PK sample available.

End point type	Secondary

End point timeframe:

Predose (Hour[hr]0), 0.5 hr after end of infusion (infusion duration=1 hr) on Cycle 1 Day 1; predose (hr 0) on Day 1 of Cycles 2, 3, 4, 8; at treatment discontinuation (up to 1 year); 90-120 days after last dose (last dose = up to 1 year) (Cycle=21 days)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics for atezolizumab were determined prior to this study. There are no statistics from this study.

End point values	Atezolizumab			
Subject group type	Reporting group			
Number of subjects analysed	85			
Units: ug/mL				
arithmetic mean (standard deviation)	34.1 (± 30.1)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline up to 90 days after last dose of study drug or until initiation of new systemic anti-cancer therapy, whichever occurs first (last dose = up to approximately 71 months)

Adverse event reporting additional description:

The safety population included all randomized participants who received any amount of study treatment, regardless of whether a full or partial dose was received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Atezolizumab

Reporting group description:

Participants received atezolizumab 1200 milligrams (mg) intravenous (IV) infusion every 3 weeks (q3w) for 16 cycles (each cycle=21 days) or 1 year (whichever occurred first).

Reporting group title	Placebo

Reporting group description:

Participants received placebo matching to atezolizumab q3w for 16 cycles (each cycle=21 days) or 1 year (whichever occurred first)

Serious adverse events	Atezolizumab	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	69 / 390 (17.69%)	46 / 383 (12.01%)	
number of deaths (all causes)	57	55	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gallbladder cancer			
subjects affected / exposed	0 / 390 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder papilloma			
subjects affected / exposed	0 / 390 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myeloid leukaemia			

subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Colorectal adenoma			
subjects affected / exposed	0 / 390 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of colon			
subjects affected / exposed	1 / 390 (0.26%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Vasculitis			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 390 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 390 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 390 (0.51%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	3 / 390 (0.77%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Death			
subjects affected / exposed	0 / 390 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ulcer			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	2 / 390 (0.51%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyp			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Immune-mediated adverse reaction			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic immune activation			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal			

disorders			
Pulmonary embolism			
subjects affected / exposed	3 / 390 (0.77%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 390 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aspiration			
subjects affected / exposed	0 / 390 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mass			
subjects affected / exposed	0 / 390 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 390 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural fever			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 390 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			

subjects affected / exposed	1 / 390 (0.26%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	0 / 390 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 390 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 390 (0.51%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	0 / 390 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 390 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			

subjects affected / exposed	0 / 390 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Presyncope			
subjects affected / exposed	0 / 390 (0.00%)	2 / 383 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 390 (0.26%)	2 / 383 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Axonal neuropathy			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			

subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 390 (0.51%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 390 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 390 (0.00%)	2 / 383 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 390 (0.51%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			

subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 390 (0.26%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Blindness unilateral			
subjects affected / exposed	0 / 390 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	2 / 390 (0.51%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 390 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 390 (0.26%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Diarrhoea			
subjects affected / exposed	3 / 390 (0.77%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	3 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eosinophilic colitis			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	3 / 390 (0.77%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 390 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 390 (0.00%)	2 / 383 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 390 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			

subjects affected / exposed	0 / 390 (0.00%)	3 / 383 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis psoriasiform			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoriasis			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 390 (0.00%)	3 / 383 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basedow's disease			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders			
Polymyositis			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	0 / 390 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Herpes ophthalmic			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pharyngeal abscess			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 390 (0.77%)	2 / 383 (0.52%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 390 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	4 / 390 (1.03%)	3 / 383 (0.78%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			

subjects affected / exposed	1 / 390 (0.26%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis aseptic			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	0 / 390 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal infection			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	0 / 390 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection viral			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 390 (0.26%)	2 / 383 (0.52%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Salpingitis			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal candidiasis			

subjects affected / exposed	0 / 390 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 390 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mediastinitis			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	1 / 390 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	5 / 390 (1.28%)	2 / 383 (0.52%)	
occurrences causally related to treatment / all	3 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Atezolizumab	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	329 / 390 (84.36%)	290 / 383 (75.72%)	
Investigations			
Weight increased			
subjects affected / exposed	11 / 390 (2.82%)	21 / 383 (5.48%)	
occurrences (all)	13	22	
Blood creatinine increased			
subjects affected / exposed	29 / 390 (7.44%)	29 / 383 (7.57%)	
occurrences (all)	36	39	
Alanine aminotransferase increased			

subjects affected / exposed	26 / 390 (6.67%)	12 / 383 (3.13%)	
occurrences (all)	29	15	
Vascular disorders			
Hypertension			
subjects affected / exposed	19 / 390 (4.87%)	36 / 383 (9.40%)	
occurrences (all)	20	41	
Nervous system disorders			
Dizziness			
subjects affected / exposed	29 / 390 (7.44%)	29 / 383 (7.57%)	
occurrences (all)	30	33	
Headache			
subjects affected / exposed	51 / 390 (13.08%)	49 / 383 (12.79%)	
occurrences (all)	65	72	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	41 / 390 (10.51%)	16 / 383 (4.18%)	
occurrences (all)	44	32	
Fatigue			
subjects affected / exposed	110 / 390 (28.21%)	93 / 383 (24.28%)	
occurrences (all)	145	124	
Influenza like illness			
subjects affected / exposed	29 / 390 (7.44%)	18 / 383 (4.70%)	
occurrences (all)	39	27	
Oedema peripheral			
subjects affected / exposed	21 / 390 (5.38%)	17 / 383 (4.44%)	
occurrences (all)	26	19	
Asthenia			
subjects affected / exposed	36 / 390 (9.23%)	26 / 383 (6.79%)	
occurrences (all)	47	28	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	24 / 390 (6.15%)	14 / 383 (3.66%)	
occurrences (all)	29	15	
Gastrointestinal disorders			
Vomiting			

subjects affected / exposed	18 / 390 (4.62%)	28 / 383 (7.31%)	
occurrences (all)	19	29	
Dry mouth			
subjects affected / exposed	26 / 390 (6.67%)	6 / 383 (1.57%)	
occurrences (all)	29	6	
Abdominal pain			
subjects affected / exposed	26 / 390 (6.67%)	23 / 383 (6.01%)	
occurrences (all)	31	24	
Diarrhoea			
subjects affected / exposed	85 / 390 (21.79%)	79 / 383 (20.63%)	
occurrences (all)	128	125	
Nausea			
subjects affected / exposed	46 / 390 (11.79%)	54 / 383 (14.10%)	
occurrences (all)	64	77	
Constipation			
subjects affected / exposed	26 / 390 (6.67%)	26 / 383 (6.79%)	
occurrences (all)	29	28	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	51 / 390 (13.08%)	48 / 383 (12.53%)	
occurrences (all)	63	51	
Dyspnoea			
subjects affected / exposed	26 / 390 (6.67%)	16 / 383 (4.18%)	
occurrences (all)	34	18	
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	25 / 390 (6.41%)	14 / 383 (3.66%)	
occurrences (all)	33	17	
Pruritus			
subjects affected / exposed	74 / 390 (18.97%)	48 / 383 (12.53%)	
occurrences (all)	94	61	
Rash			
subjects affected / exposed	46 / 390 (11.79%)	20 / 383 (5.22%)	
occurrences (all)	55	24	
Endocrine disorders			

Hyperthyroidism			
subjects affected / exposed	20 / 390 (5.13%)	4 / 383 (1.04%)	
occurrences (all)	21	4	
Hypothyroidism			
subjects affected / exposed	56 / 390 (14.36%)	12 / 383 (3.13%)	
occurrences (all)	62	13	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	43 / 390 (11.03%)	45 / 383 (11.75%)	
occurrences (all)	52	55	
Pain in extremity			
subjects affected / exposed	18 / 390 (4.62%)	20 / 383 (5.22%)	
occurrences (all)	20	24	
Arthralgia			
subjects affected / exposed	78 / 390 (20.00%)	57 / 383 (14.88%)	
occurrences (all)	101	75	
Myalgia			
subjects affected / exposed	35 / 390 (8.97%)	25 / 383 (6.53%)	
occurrences (all)	40	39	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	23 / 390 (5.90%)	26 / 383 (6.79%)	
occurrences (all)	30	32	
Upper respiratory tract infection			
subjects affected / exposed	33 / 390 (8.46%)	27 / 383 (7.05%)	
occurrences (all)	39	31	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	21 / 390 (5.38%)	16 / 383 (4.18%)	
occurrences (all)	26	16	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 September 2016	The following changes were made: [1] The Leibovich scoring system as an eligibility criterion was replaced; [2] The study population was broadened; [3] The intended sample size was adjusted; [4] The definition of a DFS event included new primary renal cell carcinoma (RCC); [5] Radiographic scans performed as part of surveillance for RCC recurrence would be submitted to central assessment for potential independent review; [6] A sample of RCC tumor with the highest tumor grade would be submitted for central review; [7] A safety evaluation visit was added at 3 months after the last dose of study treatment; [8] Detailed guidelines for investigator determination of RCC disease recurrence were added; [9] Updated safety data from a Phase Ia Study was included in the protocol; [10] DFS in participants whose tumors express IHC IC1/2/3 was added as a secondary endpoint; [11] Randomization stratification factors were changed to reflect the updated participant population; [12] The number of study sites increased; [13] Instructions for emergency unblinding of treatment assignment were provided; [14] The definition of a positive surgical margin was clarified; [15] Guidance was provided regarding the eligibility of participants with small pulmonary nodules; [16] Exclusion criteria were updated; [17] The frequency of surveillance imaging for RCC recurrence was reduced; [18] Clarification was made regarding thyroid-function testing; [19] Epstein-Barr Virus (EBV) screening sample collection was removed; [20] The timing of patient-reported outcome evaluations was clarified; [21] The instructions for the reporting of infusion-related reactions were modified; [22] The back-up Medical Monitor changed; [23] The definition of sarcomatoid RCC was clarified; [24] Additional minor changes were made to improve clarity and consistency.
16 December 2016	The following changes were made: [1] The method of assessment of the primary endpoint was changed; [2] It was specified that tumor assessments should continue until disease recurrence; [3] Assessment of imaging data by independent central radiologic review was required for confirmation of disease-free status at baseline; [4] The frequency of surveillance imaging for RCC recurrence after Year 4 was increased from annually to every 6 months; [5] Clarification that the level of stratification factors could be combined for analysis purposes; [6] Clarification that prospective protocol deviations were not allowed; [7] Pregnancy testing frequency was increased to every cycle and at the first post-treatment visit; [8] Details of the Medical Monitor and back-up Medical Monitor were updated; [9] The imaging and biopsy requirements for confirmation of disease recurrence were updated; [10] Additional minor changes were made to improve clarity and consistency.
01 March 2018	The following updates were made: [1] Section 5.1.1 was amended to align with current atezolizumab risk language; [2] Appendix 11 was added so there was no longer a need to consult the Atezolizumab Investigator's Brochure for management guidelines; [3] Additional minor changes were made to improve clarity and consistency.
20 September 2018	The following changes were made: [1] The control (placebo) arm median disease-free survival (mDFS) assumption was modified from 36 to 47 months, and the control arm median overall survival (OS) assumption was modified from 81.4 to 100 months; [2] Eligibility criteria was modified; [3] The role of the independent Data Monitoring Committee (iDMC) was amended; [4] 1- and 2-year IRF-assessed DFS rate and 1- and 2-year investigator-assessed DFS rate were added as secondary efficacy endpoints; [5] Inclusion criterion were modified; [6] The exclusionary time periods were amended; [7] Information regarding blinding of treatment assignment and circumstances for unblinding were updated; [8]

05 December 2018	The following changes were made: [1] Specified when ECG recordings were required; [2]2 Exclusion criterion were clarified; [3] Stated that premedication is "not routinely recommended" instead of "not permitted;" [4] Median disease-free survival (mDFS) assumption of the control arm was amended; [5] It was clarified that the Unblinded Medical Monitor would not be directly involved in the conduct of the clinical study; [6] The control arm mDFS and OS assumptions were modified; [7] Eligibility criteria were modified; [8] The role of the independent Data Monitoring Committee was amended; [9] 1- and 2-year IRF-assessed DFS rate and 1- and 2-year investigator-assessed DFS rate were added as secondary efficacy endpoints; [10] The exclusionary time periods were amended; [11] Information regarding blinding of treatment and unblinding was updated; [12] Clarification was made regarding the administration of infusions and timing of vital sign measurements relative; [13] Clarification of various assessments; [14] Clarification regarding timepoints for completion of patient-reported outcome questionnaires; [15] Instructions about participant withdrawal from the RBR after site closure were modified; [16] Lists of risks for atezolizumab and guidelines for managing participants who experience atezolizumab-associated AEs was revised; [17] Information regarding systemic immune activation was amended; [18] The reporting of the term "sudden death" was updated; [19] Event reporting for hospitalization was clarified; [20] Back-up and Unblinded Medical Monitor information was updated; [21] Additional language was added or updated for clarification; [22] Guidelines for the assessment of renal cell carcinoma- were amended; [23] Additional minor changes were made to improve clarity and consistency.
15 February 2020	The following changes were made: [1] "Immune-related" was changed to "immune-mediated" when describing events associated with atezolizumab; [2] Exploratory study objectives were updated; [3] Language was added for clarification; [4] The list of atezolizumab risks was updated; [5] Systemic immune activation was replaced by hemophagocytic lymphohistiocytosis and macrophage activation syndrome in the list of potential risks for atezolizumab; [6] Medical Monitor information was updated; [7] Clarification was provided on the reporting of all deaths after the AE reporting period; [8] Definition of local recurrence was updated; [9] Additional details were provided on the planned exploratory subgroup analysis of participants with tumor Fuhrman Grade 4 or sarcomatoid histology; [10] The requirement for use of a tourniquet was removed; [11] The atezolizumab AE management guidelines were revised; [12] The management guidelines for infusion-related reactions associated with atezolizumab were updated; [13] Guidelines for managing participants who experienced atezolizumab-associated AE were revised to include myositis; [14] Additional minor changes were made to improve clarity and consistency.
07 February 2021	The following changes were made: [1] Language was added to clarify endpoints associated with secondary efficacy and exploratory objectives; [2] Statistical methods updated to remove the planned interim DFS analysis and to update the total OS analyses; [3] COVID-specific information and risk language was included; [4] Clarified that the iDMC scope of evaluation was for safety data only; [5] Clarified that unblinding of treatment assignment would occur after the primary analysis of DFS; [6] Language in relation to AE reporting associated with PRO data was removed; [7] Back-up medical monitor information was updated; [8] Detailed updates associated with the removal of the planned interim DFS analysis; [9] Incorporate language associated with a sensitivity analysis that will be conducted for IRF-assessed DFS; [10] Atezo protocol SCAR language updated; [11] HLH and MAS replaced systemic inflammatory response syndrome on the list of atezolizumab-associated AEs of special interest (AESIs); [12] The management guidelines for HLH and MAS were modified; [13] Clarified that AEs associated with a special situation that also qualify as AESIs should be reported within 24 hours; [14] Clarified that sites are not expected to review the PRO data for AEs; [15] Female participants were to inform the investigator if they became pregnant per ICF instructions; [16] Correction to the Roche policy on data sharing; [17] The list of approved indications for atezolizumab was updated; [18] The management guidelines for Grade 4 myositis were removed; [19] ATA (anti-therapeutic antibody) was updated to ADA (anti-drug antibody); [20] "Immunerelated" was changed to "immune-mediated" when describing events associated with atezolizumab; [21] Additional minor changes were made to improve clarity and consistency.

12 November 2021	The following changes were made: [1] The protocol was amended to change the primary endpoint of IRF-assessed DFS to investigator-assessed DFS; [2] Benefit-risk assessment and guidance on concomitant administration of coronavirus disease 2019 vaccines with atezolizumab were modified; [3] Language was updated to change the endpoint of IRF-assessed DFS to investigator-assessed DFS; [4] The secondary efficacy endpoint of investigator-assessed DFS was changed to IRF-assessed DFS; [5] A new secondary endpoint of IRF-assessed event-free survival (EFS) was added; [6] The endpoint for immunogenicity objective, "To evaluate the immune response to atezolizumab" was updated; [7] The definition of "Distant metastasis-free survival" in secondary efficacy objective endpoint was updated; [8] One exploratory endpoint was removed; [9] The responsibilities of the Principal Investigator and the role of the Medical Monitor were clarified; [10] Language was updated to clarify the use of public record searches for survival follow-up following withdrawal of consent; [11] The Medical Monitor information was updated; [12] The name of "Serious Adverse Events (SAE)/AESI Reporting Form" was updated; [13] Language was updated to include time to clinically confirmed deterioration analysis to allow for analyzing all FKSI-19 data captured; [14] The medical term "primary biliary cirrhosis" was replaced by the term "primary biliary cholangitis;" [15] The adverse event management guidelines was updated; [16] The management guidelines referencing Grade 4 myositis were removed; [17] Additional minor changes were made to improve clarity and consistency.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The sponsor decided to terminate this study before the protocol-defined end-of-study, as permitted per protocol.

Notes: