Clinical trial results:
A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Atezolizumab (Anti-PD-L1 Antibody) as Adjuvant Therapy After Definitive Local Therapy in Patients With High-Risk Locally Advanced Squamous Cell Carcinoma of the Head and Neck

Summary

EudraCT number	2017-003302-40
Trial protocol	DE ES GB PL FR BE PT HU IT
Global end of trial date	06 March 2024

Results information

Result version number	v1 (current)
This version publication date	02 October 2024
First version publication date	02 October 2024

Trial information

Trial identification

Sponsor protocol code	WO40242

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03452137
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche Ltd.
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4058
Public contact	F. Hoffmann-La Roche Ltd., F. Hoffmann-La Roche Ltd., +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche Ltd., F. Hoffmann-La Roche Ltd., +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	06 March 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 September 2023
Global end of trial reached?	Yes
Global end of trial date	06 March 2024
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The study aims to evaluate the efficacy of atezolizumab compared with placebo after definitive local therapy in participants with high-risk locally advanced squamous cell carcinoma of the head and neck (SCCHN).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 April 2018
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	Australia: 7
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Brazil: 20
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	China: 8
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Spain: 24
Country: Number of subjects enrolled	France: 35
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Hungary: 5
Country: Number of subjects enrolled	India: 16
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	Japan: 53
Country: Number of subjects enrolled	Korea, Republic of: 10
Country: Number of subjects enrolled	Poland: 17
Country: Number of subjects enrolled	Portugal: 27
Country: Number of subjects enrolled	Russian Federation: 39
Country: Number of subjects enrolled	Thailand: 16
Country: Number of subjects enrolled	Türkiye: 7
Country: Number of subjects enrolled	Taiwan: 25
Country: Number of subjects enrolled	Ukraine: 19

Country: Number of subjects enrolled	United States: 28
Country: Number of subjects enrolled	South Africa: 5
Worldwide total number of subjects	406
EEA total number of subjects	140

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)	297
From 65 to 84 years	109
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study across 128 investigative sites in 23 countries from 03 April 2018 to 06 March 2024.

Pre-assignment

Screening details:

A total of 406 participants with locally advanced squamous cell carcinoma of the head and neck (SCCHN) were randomized in 1:1 ratio to receive either atezolizumab or placebo.

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, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received atezolizumab matching placebo, intravenous (IV) infusion on Day 1 of each 21-day cycle for 16 cycles or up to 1 year or until disease recurrence, disease progression, unacceptable toxicity, consent withdrawal, or study termination by sponsor, whichever occurred first.

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

Dosage and administration details:

Placebo, on Day 1 of each 21-day cycle as IV infusion for up to Cycle 16 or up to 1 year.

Arm title	Atezolizumab

Arm description:

Participants received atezolizumab 1200 milligrams (mg), IV infusion on Day 1 of each 21-day cycle for 16 cycles or up to 1 year or until disease recurrence, disease progression, unacceptable toxicity, consent withdrawal, or study termination by sponsor, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	RO5541267
Other name	Tecentriq, MPDL3280A
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Atezolizumab, 1200 mg, on Day 1 of each 21-day cycle as IV infusion for up to Cycle 16 or up to 1 year.

Number of subjects in period 1	Placebo	Atezolizumab
Started	203	203
Received at Least One Dose of Study Drug	203	202
Completed	0	0
Not completed	203	203
Adverse event, serious fatal	67	70
Consent withdrawn by subject	12	9
Physician decision	-	1
Study Terminated by Sponsor	120	121
Lost to follow-up	4	2

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received atezolizumab matching placebo, intravenous (IV) infusion on Day 1 of each 21-day cycle for 16 cycles or up to 1 year or until disease recurrence, disease progression, unacceptable toxicity, consent withdrawal, or study termination by sponsor, whichever occurred first.	
Reporting group title	Atezolizumab
Reporting group description:	
Participants received atezolizumab 1200 milligrams (mg), IV infusion on Day 1 of each 21-day cycle for 16 cycles or up to 1 year or until disease recurrence, disease progression, unacceptable toxicity, consent withdrawal, or study termination by sponsor, whichever occurred first.	

Reporting group values	Placebo	Atezolizumab	Total
Number of subjects	203	203	406
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	57.7	59.4	
standard deviation	± 10.1	± 8.5	-
Sex: Female, Male Units: participants			
Female	29	35	64
Male	174	168	342
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	61	68	129
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	1	2
White	135	121	256
More than one race	0	0	0
Unknown or Not Reported	6	12	18
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	13	11	24
Not Hispanic or Latino	181	183	364
Unknown or Not Reported	9	9	18
Human papilloma virus (HPV) Status Units: Subjects			
Negative	166	168	334
Positive	37	35	72
Type of Definitive Local Therapy Units: Subjects			
Primary Surgery	78	79	157
No Primary Surgery	125	124	249

Response to Definitive Local Therapy			
Responses were assessed according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1).			
Units: Subjects			
Complete Response (CR)	170	170	340
Partial Response (PR) or Stable Disease (SD)	33	33	66

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received atezolizumab matching placebo, intravenous (IV) infusion on Day 1 of each 21-day cycle for 16 cycles or up to 1 year or until disease recurrence, disease progression, unacceptable toxicity, consent withdrawal, or study termination by sponsor, whichever occurred first.

Reporting group title	Atezolizumab

Reporting group description:

Participants received atezolizumab 1200 milligrams (mg), IV infusion on Day 1 of each 21-day cycle for 16 cycles or up to 1 year or until disease recurrence, disease progression, unacceptable toxicity, consent withdrawal, or study termination by sponsor, whichever occurred first.

Primary: Investigator-Assessed Event-Free Survival (INV-assessed EFS)

End point title	Investigator-Assessed Event-Free Survival (INV-assessed EFS)

End point description:

EFS=time from randomization to first documented disease recurrence (per unequivocal radiographic evidence of local recurrence, new second primary SCCHN lesion, or development of distant metastasis), or disease progression [per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)] per assessment by investigator, or death from any cause, whichever occurred first. Progressive disease (PD)=at least a 20% increase in the sum of diameters (SOD) of target lesions, taking as reference the smallest SOD on study (including baseline). Participants without disease recurrence, progression or death at the time of analysis were censored at the time of the last tumor assessment. EFS was estimated using the Kaplan-Meier (KM) method. 99999=The upper limit of the 95% CI was not estimable for INV-EFS because there was an insufficient number of events. ITT population=all randomized participants, regardless of whether they received any of the assigned treatment.

End point type	Primary

End point timeframe:

Randomization to the first documented disease recurrence, disease progression or death from any cause, whichever occurs first (up to 5 years)

End point values	Placebo	Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203	203		
Units: months				
median (confidence interval 95%)	52.73 (41.43 to 99999)	59.47 (46.75 to 99999)		

Statistical analyses

Statistical analysis title	Placebo vs Atezolizumab

Statistical analysis description:

Stratified Analysis: The stratification factors were response to definitive local therapy, human papillomavirus (HPV) status and type of definitive local therapy as per interactive voice or web-based response system (IxRS).

Comparison groups	Atezolizumab v Placebo

Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6804
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.26

Secondary: Independent Review Facility (IRF) Assessed EFS

End point title	Independent Review Facility (IRF) Assessed EFS

End point description:

EFS was defined as the time from randomization to the first documented disease recurrence (per unequivocal radiographic evidence of local recurrence, new second primary SCCHN lesion, or development of distant metastasis), or disease progression (per RECIST v1.1) per assessment by IRF, or death from any cause, whichever occurred first. PD was defined as at least a 20% increase in the SOD of target lesions, taking as reference the smallest SOD on study (including baseline). Participants without disease recurrence, progression or death at the time of analysis were censored at the time of the last tumor assessment. EFS was estimated using the Kaplan-Meier method. ITT population included all randomized participants, regardless of whether they received any of the assigned treatment. 99999= the upper limit of the 95% CI was not estimable for IRF-EFS because there was an insufficient number of events.

End point type	Secondary

End point timeframe:

Randomization to the first documented disease recurrence, disease progression or death from any cause, whichever occurs first (up to 5 years)

End point values	Placebo	Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203	203		
Units: months				
median (confidence interval 95%)	52.73 (43.10 to 99999)	59.47 (45.17 to 99999)		

Statistical analyses

Statistical analysis title	Placebo vs Atezolizumab

Statistical analysis description:

Stratified Analysis: The stratification factors were response to definitive local therapy, HPV status and type of definitive local therapy as per interactive voice or web-based response system (IxRS).

Comparison groups	Placebo v Atezolizumab

Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9115
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.32

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. Data from participants who were alive at the time of the analysis was censored as of the last date they were known to be alive. OS was estimated using the Kaplan-Meier method. 99999= The median and lower and upper limits of the 95% CI were not estimable for OS because there was an insufficient number of events. ITT population included all randomized participants, regardless of whether they received any of the assigned treatment.

End point type	Secondary

End point timeframe:

Randomization to death from any cause (up to 5 years, 5 months)

End point values	Placebo	Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203	203		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (59.47 to 99999)		

Statistical analyses

Statistical analysis title	Placebo vs Atezolizumab

Statistical analysis description:

Stratified Analysis: The stratification factors were response to definitive local therapy, HPV status and type of definitive local therapy as per interactive voice or web-based response system (IxRS).

Comparison groups	Atezolizumab v Placebo

Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8371
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.36

Secondary: Percentage of Participants Event-Free for IRF-assessed EFS at 1, 2, 3, and 4 Years

End point title	Percentage of Participants Event-Free for IRF-assessed EFS at 1, 2, 3, and 4 Years

End point description:

EFS=time from randomization to first documented disease recurrence (per unequivocal radiographic evidence of local recurrence, new second primary SCCHN lesion/development of distant metastasis) or disease progression (per RECIST v1.1) per assessment by IRF or death from any cause, whichever occurred first. PD=at least a 20% increase in SOD of target lesions, taking as reference smallest SOD on study (including baseline). Participants without disease recurrence, progression/death at time of analysis were censored at time of last tumor assessment. KM approach was used to estimate percentage of participants who were event-free for EFS at 1, 2, 3 & 4 years. ITT population=all randomized participants, regardless of whether they received any of the assigned treatment. n=number analyzed per timepoint are unique number of participants out of all assessed participants who remain at risk for an EFS event at that timepoint. Different participants may have contributed data for each timepoint.

End point type	Secondary

End point timeframe:

From randomization to EFS event or date last known to be alive and event-free at 1, 2, 3, and 4 years

End point values	Placebo	Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203	203		
Units: percentage of participants				
number (confidence interval 95%)				
1 Year (n=143, 142)	72.59 (66.41 to 78.77)	71.92 (65.68 to 78.16)		
2 Year (n=124, 128)	65.85 (59.25 to 72.46)	66.31 (59.73 to 72.89)		
3 Year (n=108, 115)	59.87 (52.99 to 66.76)	61.07 (54.25 to 67.88)		
4 Year (n=63, 66)	54.71 (47.51 to 61.90)	54.72 (47.52 to 61.91)		

Statistical analyses

Statistical analysis title	Placebo vs Atezolizumab
Statistical analysis description: Difference in EFS Event-Free Rates at 1 year	
Comparison groups	Placebo v Atezolizumab
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8816
Method	Z test
Parameter estimate	Difference in Event Free Rate
Point estimate	-0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.45
upper limit	8.11

Statistical analysis title	Placebo vs Atezolizumab
Statistical analysis description: Difference in EFS Event-Free Rates at 2 years	
Comparison groups	Placebo v Atezolizumab
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9234
Method	Z test
Parameter estimate	Difference in Event Free Rate
Point estimate	0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.86
upper limit	9.78

Statistical analysis title	Placebo vs Atezolizumab
Statistical analysis description: Difference in EFS Event-Free Rates at 3 years	
Comparison groups	Placebo v Atezolizumab
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.809
Method	Z test
Parameter estimate	Difference in Event Free Rate
Point estimate	1.19

Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.49
upper limit	10.88

Statistical analysis title	Placebo vs Atezolizumab
Statistical analysis description:	
Difference in EFS Event-Free Rates at 4 years	
Comparison groups	Placebo v Atezolizumab
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9985
Method	Z test
Parameter estimate	Difference in Event Free Rate
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.17
upper limit	10.19

Secondary: Percentage of Participants Event-Free for INV-assessed EFS at 1, 2, 3, and 4 Years

End point title	Percentage of Participants Event-Free for INV-assessed EFS at 1, 2, 3, and 4 Years

End point description:

EFS=time from randomization to first documented disease recurrence (per unequivocal radiographic evidence of local recurrence, new second primary SCCHN lesion/development of distant metastasis)/disease progression (per RECIST v1.1) per investigator or death from any cause, whichever occurred first. PD=at least a 20% increase in SOD of target lesions, taking as reference the smallest SOD on study (including baseline). Participants without disease recurrence, progression/death at time of analysis were censored at time of last tumor assessment. KM approach was used to estimate percentage of participants who were event-free for EFS at 1, 2, 3 & 4 years. ITT population=all randomized participants, regardless of whether they received any of the assigned treatment. n=number analyzed per timepoint are unique number of participants out of all the assessed participants who remain at risk for an EFS event at that timepoint. Different participants may have contributed data for each timepoint.

End point type	Secondary

End point timeframe:

From randomization to EFS event or date last known to be alive and event-free at 1, 2, 3, and 4 years

End point values	Placebo	Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203	203		
Units: percentage of participants				
number (confidence interval 95%)				
1 Year (n=143, 151)	70.84 (64.58 to 77.10)	76.01 (70.09 to 81.93)		
2 Year (n=124, 131)	63.81 (57.17 to 70.45)	67.41 (60.90 to 73.92)		
3 Year (n=110, 118)	58.57 (51.73 to 65.41)	61.71 (54.94 to 68.49)		
4 Year (n=64, 70)	55.51 (48.49 to 62.52)	56.82 (49.75 to 63.88)		

Statistical analyses

Statistical analysis title	Placebo vs Atezolizumab
Statistical analysis description: Difference in EFS Event-Free Rates at 1 year	
Comparison groups	Placebo v Atezolizumab
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2393
Method	Z test
Parameter estimate	Difference in Event Free Rate
Point estimate	5.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.44
upper limit	13.79

Statistical analysis title	Placebo vs Atezolizumab
Statistical analysis description: Difference in EFS Event-Free Rates at 4 years	
Comparison groups	Placebo v Atezolizumab
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7967
Method	Z test
Parameter estimate	Difference in Event Free Rate
Point estimate	1.31

Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.64
upper limit	11.26

Statistical analysis title	Placebo vs Atezolizumab
Statistical analysis description: Difference in EFS Event-Free Rates at 3 years	
Comparison groups	Placebo v Atezolizumab
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5222
Method	Z test
Parameter estimate	Difference in Event Free Rate
Point estimate	3.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.49
upper limit	12.77

Statistical analysis title	Placebo vs Atezolizumab
Statistical analysis description: Difference in EFS Event-Free Rates at 2 years	
Comparison groups	Placebo v Atezolizumab
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4472
Method	Z test
Parameter estimate	Difference in Event Free Rate
Point estimate	3.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.69
upper limit	12.9

Secondary: Percentage of Participants Event-Free for OS at 2, 3, and 5 Years	
End point title	Percentage of Participants Event-Free for OS at 2, 3, and 5 Years

End point description:

OS was defined as the time from randomization to death from any cause. Data from participants who were alive at the time of the analysis was censored as of the last date they were known to be alive. Kaplan-Meier approach was used to estimate the percentage of participants who were event-free for OS at 2, 3 and 5 years. ITT population included all randomized participants, regardless of whether they received any of the assigned treatment. n indicates that number analyzed per timepoint are unique number of participants out of all the assessed participants who remain at risk for an OS event at that timepoint. Different participants may have contributed data for each timepoint.

End point type	Secondary

End point timeframe:

From randomization to OS event or date last known to be alive at 2, 3, and 5 Years

End point values	Placebo	Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203	203		
Units: percentage of participants				
number (confidence interval 95%)				
2 Year (n=157, 163)	79.23 (73.64 to 84.82)	82.00 (76.68 to 87.33)		
3 Year (n=143, 140)	73.59 (67.48 to 79.70)	72.34 (66.11 to 78.56)		
5 Year (n=6, 6)	62.00 (53.46 to 70.55)	60.93 (48.01 to 73.86)		

Statistical analyses

Statistical analysis title	Placebo vs Atezolizumab

Statistical analysis description:

Difference in OS Event-Free Rates at 2 years

Comparison groups	Placebo v Atezolizumab
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4819
Method	Z test
Parameter estimate	Difference in Event Free Rate
Point estimate	2.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.95
upper limit	10.49

Statistical analysis title	Placebo vs Atezolizumab

Statistical analysis description:

Difference in OS Event-Free Rates at 5 years

Comparison groups	Placebo v Atezolizumab
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8924
Method	Z test
Parameter estimate	Difference in Event Free Rate
Point estimate	-1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.56
upper limit	14.42

Statistical analysis title	Placebo vs Atezolizumab
Statistical analysis description:	
Difference in OS Event-Free Rates at 3 years	
Comparison groups	Placebo v Atezolizumab
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7783
Method	Z test
Parameter estimate	Difference in Event Free Rate
Point estimate	-1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.97
upper limit	7.47

Secondary: Change From Baseline in Physical Function (PF) as Assessed by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire- Core 30 (EORTC-QLQ-C30) Score

End point title	Change From Baseline in Physical Function (PF) as Assessed by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire- Core 30 (EORTC-QLQ-C30) Score

End point description:

EORTC QLQ-C30 scale uses 30 questions to assess participant functioning (physical, emotional, role, cognitive & social), symptoms (fatigue, nausea & vomiting, pain), global health/quality of life(QoL) & 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, &financial difficulties). Change in PF was assessed using PF scale: participant responses to 5 questions about daily activities (strenuous activities, long walks, short walks, bed/chair rest & needing help with eating, dressing, washing themselves/using toilet) was scored on 4-point scale (1=Not at All to 4=Very Much). Scores were linearly transformed on a scale of 0-100. High score=worst functioning. ITT population=all randomized participants, regardless of whether they received any of assigned treatment. Number analyzed=number of participants with data available for analysis. n=number of participants with data available for analysis at specified timepoint. 9999=No participants were analyzed at this timepoint.

End point type	Secondary

End point timeframe:

Baseline, Day 1 of Cycles 2 to 16 (Cycle length = 21 days); study discontinuation visit (up to 1 year); Follow-up approximately every 3 months until disease recurrence or progression (up to approximately 4.5 years)

End point values	Placebo	Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	201	200		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (Cycle 1 Day 1) (n=201, 200)	82.78 (± 16.36)	83.46 (± 16.79)		
Change at Cycle 2 Day 1 (n=195, 193)	2.40 (± 11.09)	-0.58 (± 10.54)		
Change at Cycle 3 Day 1 (n= 194, 186)	3.75 (± 12.03)	-0.13 (± 12.62)		
Change at Cycle 4 Day 1 (n=177, 179)	2.90 (± 13.00)	0.77 (± 13.42)		
Change at Cycle 5 Day 1 (n=171, 168)	4.69 (± 13.86)	1.60 (± 12.15)		
Change at Cycle 6 Day 1 (n=169, 162)	4.03 (± 12.76)	2.18 (± 13.87)		
Change at Cycle 7 Day 1 (n=162, 154)	4.33 (± 13.07)	3.56 (± 13.68)		
Change at Cycle 8 Day 1 (n= 156, 151)	4.63 (± 13.07)	3.19 (± 13.71)		
Change at Cycle 9 Day 1 (n=152, 147)	4.62 (± 13.86)	2.96 (± 14.41)		
Change at Cycle 10 Day 1 (n=148, 143)	4.41 (± 14.30)	2.12 (± 14.22)		
Change at Cycle 11 Day 1 (n=145, 139)	3.82 (± 14.20)	3.69 (± 12.43)		
Change at Cycle 12 Day 1 (n=143, 139)	4.35 (± 15.23)	3.05 (± 14.89)		
Change at Cycle 13 Day 1 (n=138, 136)	5.62 (± 13.63)	3.30 (± 15.02)		
Change at Cycle 14 Day 1 (n=134, 129)	6.73 (± 13.67)	3.20 (± 13.36)		
Change at Cycle 15 Day 1 (n=133, 124)	6.13 (± 13.11)	3.99 (± 12.92)		
Change at Cycle 16 Day 1 (n=122, 116)	5.92 (± 14.85)	4.11 (± 12.88)		
Change at Study Discontinuation (n=181, 175)	2.94 (± 16.52)	2.70 (± 14.20)		
Change at Follow Up 1 (n=51, 50)	1.47 (± 16.36)	-6.63 (± 24.41)		
Change at Follow Up 2 (n=42, 44)	-1.15 (± 18.10)	0.19 (± 17.34)		
Change at Follow Up 3 (n=35, 33)	-0.81 (± 17.17)	2.68 (± 18.75)		
Change at Follow Up 4 (n=36, 28)	-1.90 (± 18.62)	-2.56 (± 28.57)		
Change at Follow Up 5 (n=30, 21)	-2.00 (± 26.21)	-6.03 (± 35.58)		
Change at Follow Up 6 (n=30, 18)	-3.61 (± 18.08)	-3.24 (± 23.84)		
Change at Follow Up 7 (n=20, 13)	-6.75 (± 21.85)	1.54 (± 24.82)		
Change at Follow Up 8 (n=20, 11)	-13.08 (± 28.96)	1.36 (± 33.11)		
Change at Follow Up 9 (n=11, 9)	2.88 (± 14.38)	4.63 (± 17.36)		
Change at Follow Up 10 (n=7, 8)	-16.43 (± 32.50)	3.33 (± 13.80)		
Change at Follow Up 11 (n=10, 4)	-10.00 (± 35.31)	-16.67 (± 24.65)		
Change at Follow Up 12 (n=6, 4)	-6.67 (± 8.43)	0.00 (± 14.40)		
Change at Follow Up 13 (n=7, 3)	-5.71 (± 7.13)	4.44 (± 10.18)		

Change at Follow Up 14 (n=3, 1)	-17.78 (± 42.86)	-6.67 (± 0)		
Change at Follow Up 15 (n=4, 0)	-5.00 (± 6.38)	9999 (± 9999)		
Change at Follow Up 16 (n=3, 0)	2.22 (± 10.18)	9999 (± 9999)		
Change at Follow Up 17 (n=2, 0)	-3.33 (± 4.71)	9999 (± 9999)		
Change at Follow Up 18 (n=2, 0)	13.33 (± 0)	9999 (± 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Health-related Quality of Life (HRQoL) as Assessed by EORTC-QLQ-C30 Score

End point title	Change From Baseline in Health-related Quality of Life (HRQoL) as Assessed by EORTC-QLQ-C30 Score

End point description:

EORTC QLQ-C30 scale uses 30 questions to assess participant functioning (physical, emotional, role, cognitive & social), symptoms (fatigue, nausea & vomiting, pain), global health/QoL & 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea & financial difficulties). Change in HRQoL was assessed using participant responses to questions regarding Global Health Status (Q29: GHS; How would you rate your overall health during the past week?) & QoL (Q30: QoL; How would you rate your overall quality of life during the past week?) were scored on a 7-point scale (1= Very poor to 7=Excellent). Using linear transformation, raw scores are standardized. Scores range from 0-100. Higher score=better outcome. ITT population was used for analysis. Number analyzed=number of participants with data available for analysis. n=number of participants with data available for analysis at specified timepoint. 9999=No participants were analyzed at this timepoints.

End point type	Secondary

End point timeframe:

Baseline, Day 1 of Cycles 2 to 16 (Cycle length = 21 days); study discontinuation visit (up to 1 year); Follow-up approximately every 3 months until disease recurrence or progression (up to approximately 4.5 years)

End point values	Placebo	Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	198	200		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (Cycle 1 Day 1) (n= 198, 200)	66.92 (± 21.41)	67.54 (± 20.79)		
Change at Cycle 2 Day 1 (n= 192, 191)	2.99 (± 20.32)	0.09 (± 18.33)		
Change at Cycle 3 Day 1 (n= 190, 187)	4.87 (± 24.02)	0.49 (± 17.35)		
Change at Cycle 4 Day 1 (n=175, 180)	6.05 (± 21.04)	1.34 (± 17.33)		
Change at Cycle 5 Day 1 (n= 170, 168)	5.29 (± 22.80)	1.19 (± 18.25)		
Change at Cycle 6 Day 1 (n=168, 163)	4.66 (± 23.81)	3.17 (± 18.01)		
Change at Cycle 7 Day 1 (n=161, 155)	7.25 (± 21.71)	4.09 (± 17.47)		
Change at Cycle 8 Day 1 (n=155, 151)	7.58 (± 21.48)	4.25 (± 19.93)		
Change at Cycle 9 Day 1 (n=152, 147)	6.30 (± 23.20)	3.00 (± 17.93)		
Change at Cycle 10 Day 1 (n=149, 143)	7.83 (± 22.29)	3.85 (± 17.12)		
Change at Cycle 11 Day 1 (n=146, 139)	7.65 (± 21.21)	2.64 (± 17.35)		
Change at Cycle 12 Day 1 (n=145, 138)	7.47 (± 22.52)	2.60 (± 17.75)		

Change at Cycle 13 Day 1 (n=140, 136)	8.45 (± 21.37)	2.94 (± 18.41)		
Change at Cycle 14 Day 1 (n=135, 128)	6.91 (± 21.82)	3.39 (± 17.04)		
Change at Cycle 15 Day 1 (n=134, 125)	7.21 (± 21.58)	5.27 (± 18.13)		
Change at Cycle 16 Day 1 (n=123, 117)	6.30 (± 22.87)	6.05 (± 17.83)		
Change at Study Discontinuation (n=179, 177)	3.86 (± 23.64)	1.55 (± 18.41)		
Change at Follow Up 1 (n=50, 50)	1.50 (± 25.01)	-5.83 (± 25.32)		
Change at Follow Up 2 (n=41, 44)	4.67 (± 21.33)	-0.95 (± 21.73)		
Change at Follow Up 3 (n=33, 33)	-1.77 (± 18.84)	2.53 (± 18.57)		
Change at Follow Up 4 (n=34, 28)	0.74 (± 25.32)	3.87 (± 22.51)		
Change at Follow Up 5 (n=29, 21)	3.16 (± 23.19)	4.76 (± 23.36)		
Change at Follow Up 6 (n=29, 18)	6.32 (± 23.11)	1.85 (± 17.28)		
Change at Follow Up 7 (n=17, 13)	2.45 (± 23.34)	-10.26 (± 23.11)		
Change at Follow Up 8 (n=17, 11)	-8.33 (± 32.00)	2.27 (± 11.84)		
Change at Follow Up 9 (n=9, 9)	3.70 (± 17.24)	-1.85 (± 12.34)		
Change at Follow Up 10 (n=5, 8)	-15.00 (± 50.14)	9.38 (± 9.38)		
Change at Follow Up 11 (n=9, 4)	-4.63 (± 50.88)	-4.17 (± 19.84)		
Change at Follow Up 12 (n=5, 4)	20.00 (± 40.23)	-14.58 (± 20.83)		
Change at Follow Up 13 (n=6, 3)	11.11 (± 38.61)	-2.78 (± 12.73)		
Change at Follow Up 14 (n=2, 1)	8.33 (± 11.79)	-16.67 (± 0)		
Change at Follow Up 15 (n=4, 0)	14.58 (± 34.94)	9999 (± 9999)		
Change at Follow Up 16 (n=3, 0)	2.78 (± 12.73)	9999 (± 9999)		
Change at Follow Up 17 (n=2, 0)	-8.33 (± 11.79)	9999 (± 9999)		
Change at Follow Up 18 (n=2, 0)	8.33 (± 11.79)	9999 (± 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentration of Atezolizumab

End point title	Serum Concentration of Atezolizumab[1]

End point description:

Pharmacokinetic (PK)-evaluable population included all participants who received at least one dose of atezolizumab and provided at least one PK sample that was evaluable. Number analyzed is the number of participants with data available for analysis. n = number of participants with data available for analysis at the specified timepoint. Different participants may have contributed data for each timepoint. 99999 = Geometric Mean and Geometric Coefficient of Variation were not evaluable as samples were below lower limit of quantification (BLLQ).

End point type	Secondary

End point timeframe:

Predose and 0.5 hours post dose on Cycle 1 Day 1; Predose on Day 1 of Cycles 2, 4, 8, and 16 (Cycle length=21 days); study discontinuation visit (up to 1 year)

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to analyze the results only for subjects in the Atezolizumab arm who received at least one dose of atezolizumab and provided at least one PK sample that was evaluable.

End point values	Atezolizumab			
Subject group type	Reporting group			
Number of subjects analysed	194			
Units: micrograms per milliliters (ug/mL)				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1: Predose (n=187)	99999 (± 99999)			
Cycle 1 Day 1: 0.5 hours Post-dose (n=183)	447 (± 27.1)			
Cycle 2 Day 1: Predose (n=191)	99.2 (± 31.1)			
Cycle 4 Day 1: Predose (n=174)	186 (± 64.3)			
Cycle 8 Day 1: Predose (n=137)	238 (± 40.6)			
Cycle 16 Day 1: Predose (n=113)	257 (± 40.3)			
Study Discontinuation (n=170)	178 (± 141.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with at Least One Adverse Event (AE)

End point title	Number of Participants with at Least One Adverse Event (AE)

End point description:

An AE is untoward medical occurrence in participant administered a pharmaceutical product & regardless of causal relationship with this treatment. An AE can therefore be any unfavorable & unintended sign (including an abnormal laboratory finding), symptom/disease temporally associated with use of investigational product, whether or not considered related to investigational product. Safety evaluable population included all randomized participants who received any amount of the study treatment.

End point type	Secondary

End point timeframe:

From first dose of study drug until 90 days after the last dose of study drug (up to 1 year, 3 months)

End point values	Placebo	Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203	202		
Units: participants	186	192		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Number of participants positive for Treatment Emergent ADA is the number of post-baseline evaluable participants determined to have treatment induced ADA or treatment-enhanced ADA during the study period. ADA evaluable population included all randomized participants who received at least one dose of atezolizumab and who had at least one post-baseline ADA result.

End point type	Secondary

End point timeframe:

Predose on Day 1 of Cycles 1, 2, 4, 8 and 16 (Cycle length=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: This endpoint was planned to analyze the results only for subjects in the Atezolizumab arm who received at least one dose of atezolizumab and who had at least one post-baseline ADA result.

End point values	Atezolizumab			
Subject group type	Reporting group			
Number of subjects analysed	192			
Units: participants	13			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For adverse events (AEs): From first dose of study drug until 90 days after the last dose of study drug (up to 1 year, 3 months); For all-cause mortality: from randomization through the end of post-treatment survival follow-up (up to 5 years, 5 months)

Adverse event reporting additional description:

Safety-evaluable population included all randomized participants who received any amount of the study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Atezolizumab 1200 mg

Reporting group description:

Participants received atezolizumab 1200 mg, IV infusion on Day 1 of each 21-day cycle for 16 cycles or up to 1 year or until disease recurrence, disease progression, unacceptable toxicity, consent withdrawal, or study termination by sponsor, whichever occurred first.

Reporting group title	Placebo

Reporting group description:

Participants received atezolizumab matching placebo, IV infusion on Day 1 of each 21-day cycle for 16 cycles or up to 1 year or until disease recurrence, disease progression, unacceptable toxicity, consent withdrawal, or study termination by sponsor, whichever occurred first.

Serious adverse events	Atezolizumab 1200 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	32 / 202 (15.84%)	32 / 203 (15.76%)	
number of deaths (all causes)	70	69	
number of deaths resulting from adverse events	3	5	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Oesophageal carcinoma			
subjects affected / exposed	1 / 202 (0.50%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma			
subjects affected / exposed	1 / 202 (0.50%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal adenoma			

subjects affected / exposed	1 / 202 (0.50%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Gastrostomy			
subjects affected / exposed	1 / 202 (0.50%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle flap operation			
subjects affected / exposed	0 / 202 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device removal			
subjects affected / exposed	1 / 202 (0.50%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fistula repair			
subjects affected / exposed	1 / 202 (0.50%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	2 / 202 (0.99%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	1 / 2	0 / 1	
Implant site pain			
subjects affected / exposed	1 / 202 (0.50%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Stridor			

subjects affected / exposed	1 / 202 (0.50%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary thrombosis			
subjects affected / exposed	0 / 202 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary embolism			
subjects affected / exposed	0 / 202 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 202 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal necrosis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal haemorrhage			
subjects affected / exposed	1 / 202 (0.50%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal stenosis			
subjects affected / exposed	0 / 202 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal oedema			
subjects affected / exposed	1 / 202 (0.50%)	2 / 203 (0.99%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			

subjects affected / exposed	1 / 202 (0.50%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 202 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration			
subjects affected / exposed	0 / 202 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Mental disorder			
subjects affected / exposed	1 / 202 (0.50%)	0 / 203 (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 / 202 (0.50%)	0 / 203 (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 / 202 (0.50%)	0 / 203 (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			
Anastomotic stenosis			
subjects affected / exposed	0 / 202 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			

subjects affected / exposed	1 / 202 (0.50%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 202 (0.50%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoradionecrosis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural complication			
subjects affected / exposed	0 / 202 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Post procedural haemorrhage			
subjects affected / exposed	1 / 202 (0.50%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative adhesion			
subjects affected / exposed	0 / 202 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	0 / 202 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation necrosis			
subjects affected / exposed	0 / 202 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			

subjects affected / exposed	1 / 202 (0.50%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Facial paralysis			
subjects affected / exposed	0 / 202 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 202 (0.50%)	2 / 203 (0.99%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 202 (0.50%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastric haemorrhage			
subjects affected / exposed	0 / 202 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 202 (0.99%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth haemorrhage			
subjects affected / exposed	0 / 202 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salivary gland fistula			
subjects affected / exposed	1 / 202 (0.50%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toothache			

subjects affected / exposed	0 / 202 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 202 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Lichen planus			
subjects affected / exposed	1 / 202 (0.50%)	0 / 203 (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			
Nephrotic syndrome			
subjects affected / exposed	1 / 202 (0.50%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prerenal failure			
subjects affected / exposed	1 / 202 (0.50%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Soft tissue necrosis			

subjects affected / exposed	0 / 202 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	0 / 202 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	0 / 202 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 202 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 202 (0.50%)	0 / 203 (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			
Medical device site infection			
subjects affected / exposed	1 / 202 (0.50%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	0 / 202 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 202 (0.00%)	2 / 203 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epiglottitis			

subjects affected / exposed	1 / 202 (0.50%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 202 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine infection			
subjects affected / exposed	0 / 202 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection bacterial			
subjects affected / exposed	1 / 202 (0.50%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericoronitis			
subjects affected / exposed	0 / 202 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngolaryngeal abscess			
subjects affected / exposed	0 / 202 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	6 / 202 (2.97%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 202 (0.50%)	2 / 203 (0.99%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 202 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	0 / 202 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary sepsis			
subjects affected / exposed	0 / 202 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 202 (0.50%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			
subjects affected / exposed	1 / 202 (0.50%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			

subjects affected / exposed	0 / 202 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 202 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Atezolizumab 1200 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	155 / 202 (76.73%)	144 / 203 (70.94%)	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	12 / 202 (5.94%)	6 / 203 (2.96%)	
occurrences (all)	14	10	
Alanine aminotransferase increased			
subjects affected / exposed	13 / 202 (6.44%)	5 / 203 (2.46%)	
occurrences (all)	17	8	
Blood creatinine increased			
subjects affected / exposed	11 / 202 (5.45%)	7 / 203 (3.45%)	
occurrences (all)	16	7	
Weight decreased			
subjects affected / exposed	13 / 202 (6.44%)	11 / 203 (5.42%)	
occurrences (all)	15	11	
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 202 (6.93%)	11 / 203 (5.42%)	
occurrences (all)	22	11	

Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	8 / 202 (3.96%)	22 / 203 (10.84%)	
occurrences (all)	11	36	
Anaemia			
subjects affected / exposed	19 / 202 (9.41%)	18 / 203 (8.87%)	
occurrences (all)	24	21	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	29 / 202 (14.36%)	26 / 203 (12.81%)	
occurrences (all)	32	30	
Asthenia			
subjects affected / exposed	11 / 202 (5.45%)	16 / 203 (7.88%)	
occurrences (all)	20	22	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	12 / 202 (5.94%)	5 / 203 (2.46%)	
occurrences (all)	13	5	
Diarrhoea			
subjects affected / exposed	26 / 202 (12.87%)	10 / 203 (4.93%)	
occurrences (all)	40	10	
Dry mouth			
subjects affected / exposed	18 / 202 (8.91%)	16 / 203 (7.88%)	
occurrences (all)	21	16	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	17 / 202 (8.42%)	12 / 203 (5.91%)	
occurrences (all)	21	12	
Oropharyngeal pain			
subjects affected / exposed	6 / 202 (2.97%)	11 / 203 (5.42%)	
occurrences (all)	7	15	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	23 / 202 (11.39%)	15 / 203 (7.39%)	
occurrences (all)	27	17	
Rash			

subjects affected / exposed	13 / 202 (6.44%)	17 / 203 (8.37%)	
occurrences (all)	25	18	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	12 / 202 (5.94%)	5 / 203 (2.46%)	
occurrences (all)	15	5	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	54 / 202 (26.73%)	34 / 203 (16.75%)	
occurrences (all)	59	36	
Hyperthyroidism			
subjects affected / exposed	11 / 202 (5.45%)	1 / 203 (0.49%)	
occurrences (all)	11	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	22 / 202 (10.89%)	16 / 203 (7.88%)	
occurrences (all)	27	22	
Myalgia			
subjects affected / exposed	12 / 202 (5.94%)	5 / 203 (2.46%)	
occurrences (all)	13	5	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	16 / 202 (7.92%)	16 / 203 (7.88%)	
occurrences (all)	17	16	
Hypomagnesaemia			
subjects affected / exposed	6 / 202 (2.97%)	12 / 203 (5.91%)	
occurrences (all)	9	17	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 November 2017	1. Revision of EFS definition 2. Interim OS analysis added to previously planned EFS interim analysis, with related changes to sample size determination 3. Sensitivity analyses of EFS added to assess impacts of missing data, new anti-cancer therapy, loss to follow-up, discontinuation
21 February 2018	Voluntary Harmonisation Procedure and related changes, including: rationale to support treatment duration (16 cycles or up to 1 year), reduce risk of overlapping toxicities (28 days or 5 half-lives between investigational medicinal products [IMPs]), optional interim analyses removed.
01 April 2018	1. Removal of screening pelvis computer tomography (CT) or magnetic resonance imaging (MRI) 2. Addition of chest CT or MRI at every tumor assessment 3. Addition of contrast requirement for CT or MRI of head and neck, as well as chest and abdomen, with specified exceptions
15 June 2018	1. Revised timing of surgery for removal of residual disease, initiation of study treatment, and subsequent assessments 2. Additional exclusion criteria: patients who received unapproved anti-estimated glomerular filtration rate (EGFR) agents or unapproved radiotherapy, patients with current second primary SCCHN, patients who received surgery alone or radiotherapy alone 3. Testing of total carbon dioxide permitted in place of bicarbonate 4. Requirement for testing of hepatitis B virus (HBV) surface antibody removed, hepatitis B surface antigen (HBsAg) and total Hepatitis B core antibody (HBcAb) tested instead 5. Additional safety monitoring for special situations including accidental overdose and medication error 6. Voluntary Harmonisation Procedure and further related changes, including clarification of tissue sample submission after randomization
10 October 2018	1. Clarification of eligibility assessment involving clinical staging, with tumor staging and nodal staging to be assessed synchronously 2. Restructuring of inclusion criteria pertaining to prior definitive local therapy, confirmed response to prior local therapy, and absence of metastatic disease 3. Inclusion criteria were modified to allow participation of participants who undergo salvage laryngectomy, to require female contraception and abstaining from egg donation 4. Exclusion criteria were modified to exclude HPV negative participants with TX or NX or Tis, HPV positive participants with T0 or NX, participants with squamous cell carcinoma of the paranasal sinus or any carcinoma of non-squamous histology, participants who underwent prior systemic adjuvant therapy 5. Collection of patient reported outcomes (PROs) was modified to allow telephone assessment, the Quality-of-Life-Head and Neck, Module 35 Questionnaire (QLQ-H & N35) was modified to omit additional questions related to swallowing 6. Guidelines for management of AEs related to atezolizumab were revised to include nephritis 7. Clarification on treatment interruption/withholding and resumption
16 December 2019	1. Additional approved indications for atezolizumab included in background 2. Systemic immune activation replaced with hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS) 3. Atezolizumab risks and AE management guidelines updated to include myositis, HLH, and MAS; to allow longer treatment interruption and resumption of study treatment; to add laboratory testing and cardiac imaging related to myocarditis

07 January 2021	1. Investigator-assessed EFS added as primary endpoint 2. IRF-assessed EFS changed to secondary endpoint 3. Efficacy boundaries for the second interim and final OS analyses were modified 4. China extension cohort added to achieve adequate sample size for cohort-specific analysis of efficacy and safety 5. Immunosuppressive therapy removed from prohibited therapy and added to cautionary therapy to allow for use in immune-mediated adverse events 6. Identified risks and adverse events of special interest (AESIs) associated with atezolizumab were updated 7. AE management guidelines for infusion-related reactions, dermatologic reactions, myositis, cytokine release syndrome (CRS), HLH, and MAS were updated. 8. Pregnancy monitoring and investigator notification language was added
22 October 2021	1. Alignment with clinical trials regulation guidelines 2. OS changed from co-primary endpoint to key secondary endpoint to be tested if INV-EFS is positive
04 November 2021	Investigators-assessed and IRF EFS assessments at 3 and 4-year landmarks added
24 February 2023	1. OS assessment at 5-year landmark added, 1-year landmark removed 2. PRO assessments during follow up reduced to decrease participant burden 3. China extension cohort removed 4. Changed study assumptions about expected outcomes for participants with Stage III and IV SCCHN, including EFS and OS 5. COVID-19 benefit-risk assessment added 6. Futility assessment of EFS added 7. Atezolizumab AE management guidelines updated 8. Updated list of preexisting autoimmune disease and immune deficiencies excluding participants from study participation 9. HLH and MAS replaced systemic inflammatory response syndrome on list of atezolizumab-associated AESIs

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
06 March 2024	The decision to terminate the study as its primary endpoint of INV-EFS was not met at its final EFS analysis. No new safety signals were identified.	-

Notes:

Limitations and caveats

None reported