Clinical trial results:
A Phase III, Randomized, Double-Blind, Placebo-Controlled Study of Atezolizumab Plus Carboplatin and Etoposide With or Without Tiragolumab (Anti-Tigit Antibody) in Patients With Untreated Extensive-Stage Small Cell Lung Cancer

Summary

EudraCT number	2019-003301-97
Trial protocol	DE GB PL AT HU BE ES GR IT
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	11 September 2025
First version publication date	11 September 2025

Trial information

Trial identification

Sponsor protocol code	GO41767

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04256421
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4058
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
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Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	06 September 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 September 2022
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

This study will evaluate the efficacy of tiragolumab plus atezolizumab and carboplatin and etoposide (CE) compared with placebo plus atezolizumab and CE in participants with chemotherapy-naive extensive-stage small cell lung cancer (ES-SCLC).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 February 2020
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: 5
Country: Number of subjects enrolled	Austria: 9
Country: Number of subjects enrolled	Belgium: 14
Country: Number of subjects enrolled	Brazil: 9
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	Czechia: 14
Country: Number of subjects enrolled	Germany: 25
Country: Number of subjects enrolled	Spain: 29
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Greece: 17
Country: Number of subjects enrolled	Hungary: 18
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	Japan: 35
Country: Number of subjects enrolled	Korea, Republic of: 67
Country: Number of subjects enrolled	Netherlands: 16
Country: Number of subjects enrolled	New Zealand: 4
Country: Number of subjects enrolled	Poland: 52
Country: Number of subjects enrolled	Russian Federation: 18
Country: Number of subjects enrolled	Singapore: 4
Country: Number of subjects enrolled	Serbia: 15
Country: Number of subjects enrolled	Türkiye: 30
Country: Number of subjects enrolled	Taiwan: 23
Country: Number of subjects enrolled	United States: 53

Worldwide total number of subjects	490
EEA total number of subjects	215

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)	233
From 65 to 84 years	255
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

A total of 490 participants with extensive stage small cell lung cancer (SCLC) took part at 139 centers across 23 countries.

Pre-assignment

Screening details:

Participants were randomized to receive Placebo + Atezolizumab (P+A) or Tiragolumab + Atezolizumab (T+A) with carboplatin & etoposide as induction treatment followed by either P+A or T+A as maintenance treatment. 1 participant from P+A arm and 4 from T+A arm were randomized but not treated.

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	Investigator, Carer, Data analyst, Subject, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo + Atezolizumab

Arm description:

During induction treatment participants received atezolizumab, 1200 milligram (mg), followed by placebo and carboplatin, as intravenous (IV) infusion, to achieve an initial target area under the concentration-time curve (AUC) of 5 milligram/milliliter/minute (mg/mL/min) on Day 1 of each 21-day cycle for 4 cycles. Etoposide 100 milligram per square meter (mg/m^2) was also administered as IV infusion on Days 1, 2 and 3 of each 21-day cycle for 4 cycles. Participants then received maintenance treatment with atezolizumab+ placebo on Day 1 of each 21-day cycle at the same dose as during induction treatment until disease progression or loss of clinical benefit.

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 administered by IV infusion on Day 1 of each 21-day cycle.

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

Dosage and administration details:

Carboplatin was administered by IV infusion on Day 1 of each 21-day cycle for 4 cycles.

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

Dosage and administration details:

Etoposide 100 mg/m^2 administered by IV infusion on Days 1, 2 and 3 of each 21-day cycle for 4 cycles.

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

Dosage and administration details:

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

Arm title	Tiragolumab + Atezolizumab

Arm description:

During induction treatment participants received atezolizumab, 1200 mg, followed by tiragolumab, 600mg and carboplatin, as IV infusion, to achieve an initial target AUC of 5 mg/mL/min on Day 1 of each 21-day cycle for 4 cycles. Etoposide 100 mg/m^2 was also administered as IV infusion on Days 1, 2 and 3 of each 21-day cycle for 4 cycles. Participants then received maintenance treatment with atezolizumab+ tiragolumab on Day 1 of each 21-day cycle at the same dose as during induction treatment until disease progression or loss of clinical benefit.

Arm type	Experimental
Investigational medicinal product name	Tiragolumab
Investigational medicinal product code	
Other name	MTIG7192A
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Tiragolumab 600 milligrams (mg) administered by IV infusion on Day 1 of each 21-day cycle.

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

Dosage and administration details:

Etoposide 100 mg/m^2 administered by IV infusion on Days 1, 2 and 3 of each 21-day cycle for 4 cycles.

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

Dosage and administration details:

Carboplatin was administered by IV infusion on Day 1 of each 21-day cycle for 4 cycles.

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

Dosage and administration details:

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

Number of subjects in period 1	Placebo + Atezolizumab	Tiragolumab + Atezolizumab
Started	247	243
Safety-evaluable Set	246	239
Completed	0	0
Not completed	247	243
Adverse event, serious fatal	171	180
Consent withdrawn by subject	9	10
Ongoing in Study	66	52
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo + Atezolizumab

Reporting group description:

During induction treatment participants received atezolizumab, 1200 milligram (mg), followed by placebo and carboplatin, as intravenous (IV) infusion, to achieve an initial target area under the concentration-time curve (AUC) of 5 milligram/milliliter/minute (mg/mL/min) on Day 1 of each 21-day cycle for 4 cycles. Etoposide 100 milligram per square meter (mg/m^2) was also administered as IV infusion on Days 1, 2 and 3 of each 21-day cycle for 4 cycles. Participants then received maintenance treatment with atezolizumab+ placebo on Day 1 of each 21-day cycle at the same dose as during induction treatment until disease progression or loss of clinical benefit.

Reporting group title	Tiragolumab + Atezolizumab

Reporting group description:

During induction treatment participants received atezolizumab, 1200 mg, followed by tiragolumab, 600mg and carboplatin, as IV infusion, to achieve an initial target AUC of 5 mg/mL/min on Day 1 of each 21-day cycle for 4 cycles. Etoposide 100 mg/m^2 was also administered as IV infusion on Days 1, 2 and 3 of each 21-day cycle for 4 cycles. Participants then received maintenance treatment with atezolizumab+ tiragolumab on Day 1 of each 21-day cycle at the same dose as during induction treatment until disease progression or loss of clinical benefit.

Reporting group values	Placebo + Atezolizumab	Tiragolumab + Atezolizumab	Total
Number of subjects	247	243	490
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	65.1	64.5	
standard deviation	± 7.9	± 8.2	-
Sex: Female, Male Units: participants			
Female	83	81	164
Male	164	162	326

End points

End points reporting groups

Reporting group title	Placebo + Atezolizumab

Reporting group description:

During induction treatment participants received atezolizumab, 1200 milligram (mg), followed by placebo and carboplatin, as intravenous (IV) infusion, to achieve an initial target area under the concentration-time curve (AUC) of 5 milligram/milliliter/minute (mg/mL/min) on Day 1 of each 21-day cycle for 4 cycles. Etoposide 100 milligram per square meter (mg/m^2) was also administered as IV infusion on Days 1, 2 and 3 of each 21-day cycle for 4 cycles. Participants then received maintenance treatment with atezolizumab+ placebo on Day 1 of each 21-day cycle at the same dose as during induction treatment until disease progression or loss of clinical benefit.

Reporting group title	Tiragolumab + Atezolizumab

Reporting group description:

During induction treatment participants received atezolizumab, 1200 mg, followed by tiragolumab, 600mg and carboplatin, as IV infusion, to achieve an initial target AUC of 5 mg/mL/min on Day 1 of each 21-day cycle for 4 cycles. Etoposide 100 mg/m^2 was also administered as IV infusion on Days 1, 2 and 3 of each 21-day cycle for 4 cycles. Participants then received maintenance treatment with atezolizumab+ tiragolumab on Day 1 of each 21-day cycle at the same dose as during induction treatment until disease progression or loss of clinical benefit.

Primary: Investigator-Assessed Progression Free Survival (PFS) in the Primary Analysis Set (PAS)

End point title	Investigator-Assessed Progression Free Survival (PFS) in the Primary Analysis Set (PAS)

End point description:

PFS was defined as the time from randomization to the first documented disease progression (PD) as determined by the investigator with the use of Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 or death from any cause, whichever occurred first. 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). In addition to the relative increase of 20%, the SOD must also demonstrate an absolute increase of >/= 5 millimeters (mm). PAS: All randomized participants without presence or history of brain metastases at baseline.

End point type	Primary

End point timeframe:

From randomization to the first occurrence of disease progression or death from any cause, whichever occurs first (up to approximately 24 months)

End point values	Placebo + Atezolizumab	Tiragolumab + Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	201	196		
Units: months				
median (confidence interval 95%)	5.55 (5.36 to 5.85)	5.36 (4.67 to 5.52)		

Statistical analyses

Statistical analysis title	Stratified Analysis for PFS (PAS)
Statistical analysis description:	
Stratification factors were LDH (> upper limit of normal [ULN] vs. </= ULN) and Eastern Cooperative Oncology Group (ECOG; 0 vs. 1).	
Comparison groups	Placebo + Atezolizumab v Tiragolumab + Atezolizumab
Number of subjects included in analysis	397
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3504
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.38

Primary: Overall Survival (OS) in the PAS

End point title	Overall Survival (OS) in the PAS
End point description:	
OS was defined as the time from randomization to death from any cause. PAS: All randomized participants without presence or history of brain metastases at baseline.	
End point type	Primary
End point timeframe:	
From randomization to death from any cause (up to approximately 24 months)	

End point values	Placebo + Atezolizumab	Tiragolumab + Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	201	196		
Units: months				
median (confidence interval 95%)	13.14 (12.16 to 15.11)	13.11 (10.84 to 14.39)		

Statistical analyses

Statistical analysis title	Stratified Analysis for OS (PAS)
Statistical analysis description:	
Stratification factors were LDH (> ULN vs. </= ULN) and ECOG (0 vs. 1).	
Comparison groups	Placebo + Atezolizumab v Tiragolumab + Atezolizumab

Number of subjects included in analysis	397
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2859
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.44

Secondary: PFS in the FAS

End point title	PFS in the FAS

End point description:

PFS was defined as the time from randomization to the first documented PD as determined by the investigator with the use of RECIST v1.1 or death from any cause, whichever occurred first. PD: at least a 20% increase in the SOD of target lesions, taking as reference the smallest SOD on study (including baseline). In addition to the relative increase of 20%, the SOD must also demonstrate an absolute increase of >/= 5 mm. FAS: All randomized participants, whether or not the participant received the assigned treatment.

End point type	Secondary

End point timeframe:

From randomization to the first occurrence of disease progression or death from any cause, whichever occurs first (up to approximately 24 months)

End point values	Placebo + Atezolizumab	Tiragolumab + Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	243		
Units: months				
median (confidence interval 95%)	5.42 (4.47 to 5.65)	5.06 (4.40 to 5.42)		

Statistical analyses

Statistical analysis title	Stratified Analysis for PFS (FAS)

Statistical analysis description:

Stratification factors were LDH (> ULN vs. </= ULN) and ECOG (0 vs. 1).

Comparison groups	Placebo + Atezolizumab v Tiragolumab + Atezolizumab

Number of subjects included in analysis	490
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.444
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.31

Secondary: OS in the FAS

End point title	OS in the FAS

End point description:

OS was defined as the time from randomization to death from any cause. FAS: All randomized participants, whether or not the participant received the assigned treatment.

End point type	Secondary

End point timeframe:

From randomization to death from any cause (up to approximately 24 months)

End point values	Placebo + Atezolizumab	Tiragolumab + Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	243		
Units: months				
median (confidence interval 95%)	12.91 (11.99 to 14.52)	12.75 (10.84 to 14.29)		

Statistical analyses

Statistical analysis title	Stratified Analysis for OS (FAS)

Statistical analysis description:

Stratification factors were LDH (> ULN vs. </= ULN) and ECOG (0 vs. 1).

Comparison groups	Placebo + Atezolizumab v Tiragolumab + Atezolizumab
Number of subjects included in analysis	490
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4205
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.09

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	1.35

Secondary: Investigator-Assessed Confirmed Objective Response Rate (ORR) in the PAS

End point title	Investigator-Assessed Confirmed Objective Response Rate (ORR) in the PAS

End point description:

ORR was defined as the percentage of participants with a complete response (CR) or a partial response (PR) as determined by the investigator with the use of RECIST v1.1. CR was defined as disappearance of all target lesions or any pathological lymph nodes must have reduction in short axis to < 10 mm. PR was defined as at least a 30% decrease in the SOD of all target lesions, taking as reference the baseline SOD, in the absence of CR. PAS: All randomized participants without presence or history of brain metastases at baseline.

End point type	Secondary

End point timeframe:

From randomization up to approximately 24 months

End point values	Placebo + Atezolizumab	Tiragolumab + Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	201	196		
Units: percentage of participants				
number (confidence interval 95%)	66.7 (59.64 to 73.05)	73.5 (66.61 to 79.39)		

Statistical analyses

Statistical analysis title	Stratified Analysis for ORR (PAS)

Statistical analysis description:

Stratification factors were LDH (> ULN vs. </= ULN) and ECOG (0 vs. 1).

Comparison groups	Placebo + Atezolizumab v Tiragolumab + Atezolizumab
Number of subjects included in analysis	397
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1418
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Overall Response Rates
Point estimate	6.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.57
upper limit	15.99

Secondary: Investigator-Assessed Confirmed ORR in the FAS

End point title	Investigator-Assessed Confirmed ORR in the FAS

End point description:

ORR was defined as the percentage of participants with CR or PR as determined by the investigator with the use of RECIST v1.1. CR was defined as disappearance of all target lesions or any pathological lymph nodes must have reduction in short axis to < 10 mm. PR was defined as at least a 30% decrease in the SOD of all target lesions, taking as reference the baseline SOD, in the absence of CR. FAS: All randomized participants, whether or not the participant received the assigned treatment.

End point type	Secondary

End point timeframe:

From randomization up to approximately 24 months

End point values	Placebo + Atezolizumab	Tiragolumab + Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	243		
Units: percentage of participants				
number (confidence interval 95%)	65.6 (59.26 to 71.42)	70.8 (64.56 to 76.33)		

Statistical analyses

Statistical analysis title	Stratified Analysis for ORR (FAS)

Statistical analysis description:

Stratification factors were LDH (> ULN vs. </= ULN) and ECOG (0 vs. 1).

Comparison groups	Placebo + Atezolizumab v Tiragolumab + Atezolizumab
Number of subjects included in analysis	490
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2191
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Overall Response Rates
Point estimate	5.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.33
upper limit	13.61

Secondary: Investigator-Assessed Duration of Response (DOR) in the PAS

End point title	Investigator-Assessed Duration of Response (DOR) in the PAS

End point description:

DOR was defined as the time from the first occurrence of a documented objective response (OR) to PD or death from any cause, whichever occurred first, as determined by the investigator with the use of RECIST v1.1. CR: was defined as disappearance of all target lesions or any pathological lymph nodes must have reduction in short axis to < 10 mm PR was defined as at least a 30% decrease in the SOD of all target lesions, taking as reference the baseline SOD, in the absence of CR. PD= at least a 20% increase in the SOD of target lesions, taking as reference the smallest SOD on study (including baseline). In addition to the relative increase of 20%, the SOD must also demonstrate an absolute increase of >/= 5 mm. PAS: All randomized participants without presence or history of brain metastases at baseline.

End point type	Secondary

End point timeframe:

From the first occurrence of a documented confirmed objective response to disease progression or death from any cause, whichever occurs first (up to approximately 24 months)

End point values	Placebo + Atezolizumab	Tiragolumab + Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134[1]	144[2]		
Units: months				
median (confidence interval 95%)	5.59 (4.57 to 6.93)	4.19 (4.14 to 4.60)		

Notes:

[1] - DOR was analyzed in confirmed responders by investigator.

[2] - DOR was analyzed in confirmed responders by investigator.

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator-Assessed DOR in the FAS

End point title	Investigator-Assessed DOR in the FAS

End point description:

DOR was defined as the time from the first occurrence of a documented OR to PD or death from any cause, whichever occurred first, as determined by the investigator with the use of RECIST v1.1. CR: was defined as disappearance of all target lesions or any pathological lymph nodes must have reduction in short axis to < 10 mm PR was defined as at least a 30% decrease in the SOD of all target lesions, taking as reference the baseline SOD, in the absence of CR. PD= at least a 20% increase in the SOD of target lesions, taking as reference the smallest SOD on study (including baseline). In addition to the relative increase of 20%, the SOD must also demonstrate an absolute increase of >/= 5 mm. FAS: All randomized participants, whether or not the participant received the assigned treatment.

End point type	Secondary

End point timeframe:

From the first occurrence of a documented confirmed objective response to disease progression or death from any cause, whichever occurs first (up to approximately 24 months)

End point values	Placebo + Atezolizumab	Tiragolumab + Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162[3]	172[4]		
Units: months				
median (confidence interval 95%)	5.11 (4.37 to 5.75)	4.17 (4.07 to 4.37)		

Notes:

[3] - DOR was analyzed in confirmed responders by investigator.

[4] - DOR was analyzed in confirmed responders by investigator.

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator-Assessed PFS Rates at 6 Months and 12 Months in the PAS

End point title	Investigator-Assessed PFS Rates at 6 Months and 12 Months in the PAS

End point description:

PFS rate at 6 months and 12 months was defined as the percentage of participants who were event free at these specific time points. PAS: All randomized participants without presence or history of brain metastases at baseline. Number analyzed is the number of participants with data available for analyses. n= number of participants with data available for analyses at the specified timepoints.

End point type	Secondary

End point timeframe:

Month 6, Month 12

End point values	Placebo + Atezolizumab	Tiragolumab + Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	67		
Units: percentage of participants				
number (confidence interval 95%)				
Month 6 (n= 84, 67)	42.42 (35.54 to 49.31)	35.15 (28.41 to 41.90)		
Month 12 (n= 26, 17)	17.29 (11.90 to 22.69)	14.21 (9.06 to 19.35)		

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator-Assessed PFS Rates at 6 Months and 12 Months in the FAS

End point title	Investigator-Assessed PFS Rates at 6 Months and 12 Months in the FAS

End point description:

PFS rate at 6 months and 12 months was defined as the percentage of participants who were event free at these specific time points. FAS: All randomized participants, whether or not the participant received the assigned treatment. Number analyzed is the number of participants with data available for analyses. n= number of participants with data available for analyses at the specified timepoints.

End point type	Secondary
End point timeframe: Month 6, Month 12	

End point values	Placebo + Atezolizumab	Tiragolumab + Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	74		
Units: percentage of participants				
number (confidence interval 95%)				
Month 6 (n= 92, 74)	37.95 (31.85 to 44.05)	31.30 (25.41 to 37.19)		
Month 12 (n= 26, 18)	14.07 (9.59 to 18.55)	12.33 (7.90 to 16.75)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival Rates at 12 Months and 24 Months in the PAS

End point title	Overall Survival Rates at 12 Months and 24 Months in the PAS
End point description: Overall survival rate at 12 months and 24 months was defined as the percentage of participants who were alive at these specific time points. PAS: All randomized participants without presence or history of brain metastases at baseline. Number analyzed is the number of participants with data available for analyses. n= number of participants with data available for analyses at the specified timepoints.	
End point type	Secondary
End point timeframe: Month 12, Month 24	

End point values	Placebo + Atezolizumab	Tiragolumab + Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	103		
Units: percentage of participants				
number (confidence interval 95%)				
Month 12 (n= 112, 103)	57.74 (50.82 to 64.66)	54.00 (46.97 to 61.03)		
Month 24 (n= 12, 10)	27.68 (20.43 to 34.94)	19.56 (13.16 to 25.96)		

Statistical analyses

Statistical analysis title	Month 12
Comparison groups	Placebo + Atezolizumab v Tiragolumab + Atezolizumab
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.458
Method	Z-test
Parameter estimate	Difference in Event Free Rate
Point estimate	-3.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.6
upper limit	6.13

Statistical analysis title	Month 24
Comparison groups	Placebo + Atezolizumab v Tiragolumab + Atezolizumab
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0999
Method	Z-test
Parameter estimate	Difference in Event Free Rate
Point estimate	-8.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.8
upper limit	1.55

Secondary: Overall Survival Rates at 12 Months and 24 Months in the FAS

End point title	Overall Survival Rates at 12 Months and 24 Months in the FAS

End point description:

Overall survival rate at 12 months and 24 months was defined as the percentage of participants who were alive at these specific time points. FAS: All randomized participants, whether or not the participant received the assigned treatment. Number analyzed is the number of participants with data available for analyses. n= number of participants with data available for analyses at the specified timepoints.

End point type	Secondary

End point timeframe:

Month 12, Month 24

End point values	Placebo + Atezolizumab	Tiragolumab + Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	243		
Units: percentage of participants				
number (confidence interval 95%)				
Month 12 (n= 133, 125)	55.84 (49.58 to 62.10)	52.82 (46.49 to 59.15)		
Month 24 (n= 12, 10)	25.82 (19.19 to 32.46)	20.53 (14.54 to 26.52)		

Statistical analyses

Statistical analysis title	Month 24
Comparison groups	Placebo + Atezolizumab v Tiragolumab + Atezolizumab
Number of subjects included in analysis	490
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2458
Method	Z-test
Parameter estimate	Difference in Event Free Rate
Point estimate	-5.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.23
upper limit	3.65

Statistical analysis title	Month 12
Comparison groups	Placebo + Atezolizumab v Tiragolumab + Atezolizumab
Number of subjects included in analysis	490
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5059
Method	Z-test
Parameter estimate	Difference in Event Free Rate
Point estimate	-3.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.92
upper limit	5.88

Secondary: Time to Confirmed Deterioration (TTCD) of European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core

(QLQ-C30) Physical Functioning in the PAS

End point title	Time to Confirmed Deterioration (TTCD) of European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core (QLQ-C30) Physical Functioning in the PAS

End point description:

TTCD= time from randomization until the first confirmed clinically meaningful deterioration in physical functioning.TTCD was determined based on patient-reported physical functioning (items 1-5) as collected & measured by the EORTC QLQ-C30.PF is measured on 4-point scale (1='Not at all' to 4='Very much').A high score for the physical function subscale= a high/healthy level of functioning. The scale was linearly transformed so that each score ranged from 0-100. A score change of at least 10-point in physical functioning subscale score was perceived by participants as clinically meaningful. Confirmed clinically meaningful deterioration= clinically meaningful decrease from baseline that was held for at least two consecutive assessments/ an initial clinically meaningful decrease from baseline followed by death from any cause within 3 weeks. PAS: All randomized participants without presence or history of brain metastases at baseline.9999=not estimable due to insufficient number of events.

End point type	Secondary

End point timeframe:

From randomization until the first confirmed clinically meaningful deterioration up to approximately 24 months

End point values	Placebo + Atezolizumab	Tiragolumab + Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	201	196		
Units: months				
median (confidence interval 95%)	19.35 (19.35 to 9999)	15.67 (12.81 to 9999)		

Statistical analyses

Statistical analysis title	Stratified Analysis for TTCD Physical (PAS)

Statistical analysis description:

Stratification factors were LDH (> ULN vs. </= ULN) and ECOG (0 vs. 1).

Comparison groups	Placebo + Atezolizumab v Tiragolumab + Atezolizumab
Number of subjects included in analysis	397
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9819
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.48

Secondary: TTCD of EORTC QLQ-C30 Physical Functioning in the FAS

End point title	TTCD of EORTC QLQ-C30 Physical Functioning in the FAS

End point description:

TTCD= time from randomization until the first confirmed clinically meaningful deterioration in physical functioning.TTCD was determined based on patient-reported physical functioning (items 1-5) as collected & measured by the EORTC QLQ-C30.PF is measured on 4-point scale (1='Not at all' to 4='Very much').A high score for the physical function subscale= a high/healthy level of functioning.The scale was linearly transformed so that each score ranged from 0-100.A score change of at least 10-point in physical functioning subscale score was perceived by participants as clinically meaningful.Confirmed clinically meaningful deterioration= clinically meaningful decrease from baseline that was held for at least two consecutive assessments/ an initial clinically meaningful decrease from baseline followed by death from any cause within 3 weeks.FAS: All randomized participants, whether or not the participant received the assigned treatment.9999=not estimable due to insufficient number of events.

End point type	Secondary

End point timeframe:

From randomization until the first confirmed clinically meaningful deterioration up to approximately 24 months

End point values	Placebo + Atezolizumab	Tiragolumab + Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	243		
Units: months				
median (confidence interval 95%)	19.35 (12.42 to 9999)	15.67 (11.83 to 9999)		

Statistical analyses

Statistical analysis title	Stratified Analysis for TTCD Physical (FAS)

Statistical analysis description:

Stratification factors were LDH (> ULN vs. </= ULN) and ECOG (0 vs. 1).

Comparison groups	Placebo + Atezolizumab v Tiragolumab + Atezolizumab
Number of subjects included in analysis	490
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5122
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.55

Secondary: TTCD of EORTC QLQ-C30 Global Health Status (GHS)/Quality of Life (QoL) in the PAS

End point title	TTCD of EORTC QLQ-C30 Global Health Status (GHS)/Quality of Life (QoL) in the PAS

End point description:

TTCD=time from randomization until the first confirmed clinically meaningful deterioration in patient-reported GHS/ QoL.TTCD was determined based on patient-reported GHS/QoL (items 29-30) as collected & measured by the EORTC QLQ-C30.HS/QoL items are scored on a 7-point scale that ranges from "very poor" to "excellent".A high score for the GHS/QoL subscale represented a high health related quality of life. The scale was linearly transformed so that each score ranged from 0-100. A score change of at least 10-point in GHS/QoL subscale score was perceived by participants as clinically meaningful. Confirmed clinically meaningful deterioration= clinically meaningful decrease from baseline that was held for at least 2 consecutive assessments/ an initial clinically meaningful decrease from baseline followed by death from any cause within 3 weeks. PAS: All randomized participants without presence/history of brain metastases at baseline. 9999=not estimable due to insufficient number of events.

End point type	Secondary

End point timeframe:

From randomization until the first confirmed clinically meaningful deterioration up to approximately 24 months

End point values	Placebo + Atezolizumab	Tiragolumab + Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	201	196		
Units: months				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (14.55 to 9999)		

Statistical analyses

Statistical analysis title	Stratified Analysis for TTCD GHS/QoL (PAS)

Statistical analysis description:

Stratification factors were LDH (> ULN vs. </= ULN) and ECOG (0 vs. 1).

Comparison groups	Placebo + Atezolizumab v Tiragolumab + Atezolizumab
Number of subjects included in analysis	397
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3614
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.79

Secondary: TTCD of EORTC QLQ-C30 GHS/QoL in the FAS

End point title	TTCD of EORTC QLQ-C30 GHS/QoL in the FAS

End point description:

TTCD=time from randomization until the first confirmed clinically meaningful deterioration in patient-reported GHS/ QoL.TTCD was determined based on patient-reported GHS/QoL (items 29-30) as collected & measured by the EORTC QLQ-C30.HS/QoL items are scored on a 7-point scale that ranges from "very poor" to "excellent".A high score for the GHS/QoL subscale represented a high health related quality of life. The scale was linearly transformed so that each score ranged from 0-100. A score change of at least 10-point in GHS/QoL subscale score was perceived by participants as clinically meaningful. Confirmed clinically meaningful deterioration= clinically meaningful decrease from baseline that was held for at least 2 consecutive assessments/ an initial clinically meaningful decrease from baseline followed by death from any cause within 3 weeks. FAS: All randomized participants, whether the participant received the assigned treatment. 9999=not estimable due to insufficient number of events.

End point type	Secondary

End point timeframe:

From randomization until the first confirmed clinically meaningful deterioration up to approximately 24 months

End point values	Placebo + Atezolizumab	Tiragolumab + Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	243		
Units: months				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (14.55 to 9999)		

Statistical analyses

Statistical analysis title	Stratified Analysis for TTCD GHS/QoL (FAS)

Statistical analysis description:

Stratification factors were LDH (> ULN vs. </= ULN) and ECOG (0 vs. 1).

Comparison groups	Placebo + Atezolizumab v Tiragolumab + Atezolizumab
Number of subjects included in analysis	490
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1681
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.84

Secondary: Minimum Serum Concentration (Cmin) of Tiragolumab

End point title	Minimum Serum Concentration (Cmin) of Tiragolumab[5]

End point description:

PK-evaluable set: All participants who received at least one dose of study treatment and who had at least one post-baseline PK sample available. n= number of participants with data available for analyses

at the specified timepoints.

End point type	Secondary

End point timeframe:

At the end of each cycle (each cycle is 21 days) of Cycles 1, 2, 3, 7, 11 and 15

Notes:

[5] - 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: Endpoint is reporting data only for the Tiragolumab arm.

End point values	Tiragolumab + Atezolizumab			
Subject group type	Reporting group			
Number of subjects analysed	218			
Units: microgram/milliliter (mcg/mL)				
geometric mean (geometric coefficient of variation)				
Cycle 1, n=218	29.5 (± 49.2)			
Cycle 2, n=213	46.5 (± 47.5)			
Cycle 3, n=201	56.3 (± 83.5)			
Cycle 7, n=111	76.3 (± 48.2)			
Cycle 11, n=45	78.8 (± 246)			
Cycle 15, n=17	96.4 (± 43.8)			

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 is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), 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 adverse events.

End point type	Secondary

End point timeframe:

Up to 65 months

End point values	Placebo + Atezolizumab	Tiragolumab + Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: percentage of participants				
number (not applicable)				

Notes:

[6] - Final analysis to be reported after study completion.

[7] - Final analysis to be reported after study completion.

Statistical analyses

No statistical analyses for this end point

Secondary: Cmin of Atezolizumab

End point title	Cmin of Atezolizumab

End point description:

PK-evaluable set: All participants who received at least one dose of study treatment and who had at least one post-baseline PK sample available. Number analyzed is the number of participants with data available for analyses. n= number of participants with data available for analyses at the specified timepoints.

End point type	Secondary

End point timeframe:

At the end of each cycle (each cycle is 21 days) of Cycles 1, 2, 3, 7, 11 and 15

End point values	Placebo + Atezolizumab	Tiragolumab + Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226	217		
Units: mcg/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1, n=226, 217	75.0 (± 63.2)	75.4 (± 70.8)		
Cycle 2, n=221, 213	121 (± 55.8)	125 (± 38.4)		
Cycle 3, n=200, 198	144 (± 49.8)	155 (± 81.5)		
Cycle 7, n=115, 110	205 (± 45.3)	198 (± 46.4)		
Cycle 11, n=52, 45	226 (± 37.3)	244 (± 37)		
Cycle 15, n=26, 17	198 (± 75.5)	253 (± 36.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Serum Concentration (Cmax) of Tiragolumab

End point title	Maximum Serum Concentration (Cmax) of Tiragolumab[8]

End point description:

PK-evaluable set: All participants who received at least one dose of study treatment and who had at least one post-baseline PK sample available. Number analyzed is the number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

Predose and 30 minutes post end of infusion (EOI) on Day 1 of Cycle 1 (each cycle is 21 days)

Notes:

[8] - 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: Endpoint is reporting data only for the Tiragolumab arm.

End point values	Tiragolumab + Atezolizumab			
Subject group type	Reporting group			
Number of subjects analysed	213			
Units: mcg/mL				
geometric mean (geometric coefficient of variation)	188 (± 24.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax of Atezolizumab

End point title	Cmax of Atezolizumab

End point description:

End point type	Secondary

End point timeframe:

Predose and 30 minutes post EOI on Day 1 of Cycle 1 (each cycle is 21 days)

End point values	Placebo + Atezolizumab	Tiragolumab + Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	233	224		
Units: mcg/mL				
geometric mean (geometric coefficient of variation)	398 (± 28.2)	405 (± 23.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Anti-Drug Antibodies (ADAs) to Tiragolumab

End point title	Number of Participants With Anti-Drug Antibodies (ADAs) to Tiragolumab[9]

End point description:

Reported here=number of participants who had a positive ADA assay result at baseline & number of participants positive for treatment emergent ADAs. Participants positive for treatment emergent ADAs include treatment-induced & treatment-enhanced ADA positive participants. Treatment-induced ADAs are participants with negative/missing baseline ADA result(s) & at least one positive post-baseline ADA result. Treatment-enhanced ADAs are participants with a positive ADA result at baseline who had one or

more post-baseline titer results that were at least 0.60 t.u. greater than the baseline titer result.Total number of participants who developed ADAs to tiragolumab was determined by summing the ADA-positive participants across all timepoints. Tiragolumab ADA-evaluable set: All participants who received at least one dose of tiragolumab treatment & with an ADA assay result from at least one sample result.n=number of participants with data available for analyses at the specified timepoints.

End point type	Secondary

End point timeframe:

Predose on Day 1 of Cycles 1 (each cycle is 21 days), 2, 3, 4, 8,12 and 16 and at treatment discontinuation (TD) visit (up to 24 months)

Notes:

[9] - 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: Endpoint is reporting data only for the Tiragolumab arm.

End point values	Tiragolumab + Atezolizumab			
Subject group type	Reporting group			
Number of subjects analysed	235			
Units: participants				
Positive Sample at Baseline (n=235)	2			
Positive for Treatment Emergent ADAs (n=229)	3			
Treatment-induced ADAs (n=229)	3			
Treatment-enhanced ADAs (n=229)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With ADAs to Atezolizumab

End point title	Number of Participants With ADAs to Atezolizumab

End point description:

Reported here=number of participants who had a positive ADA assay result at baseline & number of participants positive for treatment emergent ADAs. Participants positive for treatment emergent ADAs include treatment-induced & treatment-enhanced ADA positive participants. Treatment-induced ADAs are participants with negative/missing baseline ADA result(s) & at least one positive post-baseline ADA result. Treatment-enhanced ADAs are participants with a positive ADA result at baseline who had one or more post-baseline titer results that were at least 0.60 t.u. greater than the baseline titer result.Total number of participants who developed ADAs to tiragolumab was determined by summing the ADA-positive participants across all timepoints. Atezolizumab ADA-evaluable set: All participants who received at least one dose of atezolizumab treatment & with an ADA assay result from at least one sample result.n=number of participants with data available for analyses at the specified timepoints.

End point type	Secondary

End point timeframe:

Predose on Day 1 of Cycles 1 (each cycle is 21 days), 2, 3, 4, 8,12 and 16 and at TD visit (up to 24 months)

End point values	Placebo + Atezolizumab	Tiragolumab + Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	244	236		
Units: participants				
Positive Sample at Baseline (n=244,236)	2	1		
Positive for Treatment Emergent ADAs (n=238,228)	48	22		
Treatment-induced ADAs(n=238,228)	48	22		
Treatment-enhanced ADAs (n=238,228)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in EuroQol 5-Dimension, 5-Level (EQ-5D-5L) Index-based and Visual Analog Scale Scores

End point title	Change from Baseline in EuroQol 5-Dimension, 5-Level (EQ-5D-5L) Index-based and Visual Analog Scale Scores

End point description:

The EQ-5D-5L is a validated self-report health status questionnaire that was used to calculate a health status utility score for use in health economic analyses. There were two components to the EQ-5D-5L: a five-item health state profile that assessed mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analog scale (VAS) that measured health state. The EQ VAS records the participant's self-rated health on a vertical visual analogue scale ranging from 0 to 100 A single composite score was calculated based on the responses as an indicator of the participant's health status. The scale ranges 0-100, 0=worst health and 100=best health.

End point type	Secondary

End point timeframe:

From baseline up to 65 months

End point values	Placebo + Atezolizumab	Tiragolumab + Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[10]	0[11]		
Units: score on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[10] - Final analysis to be reported after study completion.

[11] - Final analysis to be reported after study completion.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 24 months

Adverse event reporting additional description:

All-cause mortality: FAS: All randomized participants, whether or not the participant received the assigned treatment. SAE and nSAE: Safety-evaluable set included all randomized participants who received at least one dose of study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Tiragolumab + Atezolizumab

Reporting group description:

During induction treatment participants received atezolizumab, 1200 mg, followed by tiragolumab, 600mg and carboplatin, as IV infusion, to achieve an initial target AUC of 5 mg/mL/min on Day 1 of each 21-day cycle for 4 cycles. Etoposide 100 mg/m^2 was also administered as IV infusion on Days 1, 2 and 3 of each 21-day cycle for 4 cycles. Participants will then receive maintenance treatment with atezolizumab+ tiragolumab on Day 1 of each 21-day cycle at the same dose as during induction treatment until disease progression or loss of clinical benefit.

Reporting group title	Placebo + Atezolizumab

Reporting group description:

During induction treatment participants received atezolizumab, 1200 mg, followed by placebo and carboplatin, as IV infusion, to achieve an initial target AUC of 5 mg/mL/min on Day 1 of each 21-day cycle for 4 cycles. Etoposide 100 mg/m^2 was also administered as IV infusion on Days 1, 2 and 3 of each 21-day cycle for 4 cycles. Participants will then receive maintenance treatment with atezolizumab+ placebo on Day 1 of each 21-day cycle at the same dose as during induction treatment until disease progression or loss of clinical benefit.

Serious adverse events	Tiragolumab + Atezolizumab	Placebo + Atezolizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	108 / 239 (45.19%)	104 / 246 (42.28%)	
number of deaths (all causes)	180	171	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	0 / 239 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Jugular vein thrombosis			

subjects affected / exposed	0 / 239 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 239 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 246 (0.41%)	
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			
General physical health deterioration			
subjects affected / exposed	1 / 239 (0.42%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			

subjects affected / exposed	0 / 239 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Asthenia			
subjects affected / exposed	2 / 239 (0.84%)	3 / 246 (1.22%)	
occurrences causally related to treatment / all	2 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 239 (0.42%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	2 / 239 (0.84%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (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			
Chronic obstructive pulmonary disease			
subjects affected / exposed	3 / 239 (1.26%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute respiratory failure			

subjects affected / exposed	1 / 239 (0.42%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 239 (0.84%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 239 (0.42%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated lung disease			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract haemorrhage			
subjects affected / exposed	0 / 239 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 239 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			

subjects affected / exposed	2 / 239 (0.84%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pneumothorax			
subjects affected / exposed	0 / 239 (0.00%)	1 / 246 (0.41%)	
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 / 239 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 239 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 239 (0.42%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	2 / 2	
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 239 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Mental status changes			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental disorder			
subjects affected / exposed	1 / 239 (0.42%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			

subjects affected / exposed	2 / 239 (0.84%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	2 / 239 (0.84%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 239 (0.42%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 239 (0.42%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 239 (0.84%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	4 / 239 (1.67%)	4 / 246 (1.63%)	
occurrences causally related to treatment / all	4 / 4	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	2 / 239 (0.84%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	3 / 239 (1.26%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	3 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			

subjects affected / exposed	0 / 239 (0.00%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 239 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 239 (0.42%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 239 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 239 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	0 / 239 (0.00%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (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	0 / 239 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			

subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	0 / 239 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 239 (0.00%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atrioventricular block complete			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	3 / 239 (1.26%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			

subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	0 / 239 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 239 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 239 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	0 / 239 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 239 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 239 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Loss of consciousness			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Motor dysfunction			

subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Limbic encephalitis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 239 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypoaesthesia			
subjects affected / exposed	0 / 239 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 239 (0.00%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Guillain-Barre syndrome			
subjects affected / exposed	1 / 239 (0.42%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	3 / 239 (1.26%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (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 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral venous sinus thrombosis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 239 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Balance disorder			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuromyotonia			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ataxia			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (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	0 / 239 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			

subjects affected / exposed	0 / 239 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	2 / 239 (0.84%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	2 / 239 (0.84%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	3 / 239 (1.26%)	5 / 246 (2.03%)	
occurrences causally related to treatment / all	2 / 3	5 / 5	
deaths causally related to treatment / all	0 / 0	1 / 1	
Febrile neutropenia			
subjects affected / exposed	16 / 239 (6.69%)	14 / 246 (5.69%)	
occurrences causally related to treatment / all	15 / 17	15 / 15	
deaths causally related to treatment / all	0 / 0	1 / 1	
Bicytopenia			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	9 / 239 (3.77%)	8 / 246 (3.25%)	
occurrences causally related to treatment / all	9 / 10	9 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			

subjects affected / exposed	1 / 239 (0.42%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 239 (0.42%)	4 / 246 (1.63%)	
occurrences causally related to treatment / all	0 / 1	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 239 (0.42%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune colitis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	2 / 239 (0.84%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			

subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated enterocolitis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 239 (0.00%)	1 / 246 (0.41%)	
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 / 239 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 239 (0.42%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	1 / 239 (0.42%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Liver disorder			
subjects affected / exposed	0 / 239 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated hepatitis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatorenal syndrome			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatitis			
subjects affected / exposed	1 / 239 (0.42%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (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			
Nephrolithiasis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	2 / 239 (0.84%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	

Endocrine disorders			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 239 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthyroidism			
subjects affected / exposed	0 / 239 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adrenal insufficiency			
subjects affected / exposed	2 / 239 (0.84%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoporosis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 246 (0.41%)	
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	0 / 239 (0.00%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 239 (0.00%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Candida sepsis			

subjects affected / exposed	0 / 239 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	3 / 239 (1.26%)	7 / 246 (2.85%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 3	0 / 3	
COVID-19			
subjects affected / exposed	6 / 239 (2.51%)	9 / 246 (3.66%)	
occurrences causally related to treatment / all	0 / 6	0 / 9	
deaths causally related to treatment / all	0 / 2	0 / 1	
Bronchitis			
subjects affected / exposed	2 / 239 (0.84%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 239 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 239 (0.42%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			

subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	1 / 239 (0.42%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 239 (0.42%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 239 (1.26%)	3 / 246 (1.22%)	
occurrences causally related to treatment / all	0 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	7 / 239 (2.93%)	12 / 246 (4.88%)	
occurrences causally related to treatment / all	1 / 8	2 / 15	
deaths causally related to treatment / all	0 / 1	1 / 2	
Pneumonia aspiration			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	6 / 239 (2.51%)	3 / 246 (1.22%)	
occurrences causally related to treatment / all	3 / 6	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Upper respiratory tract infection			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 246 (0.41%)	
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	9 / 239 (3.77%)	4 / 246 (1.63%)	
occurrences causally related to treatment / all	1 / 17	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	0 / 239 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			

subjects affected / exposed	1 / 239 (0.42%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 239 (0.42%)	0 / 246 (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	Tiragolumab + Atezolizumab	Placebo + Atezolizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	228 / 239 (95.40%)	233 / 246 (94.72%)	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	23 / 239 (9.62%)	34 / 246 (13.82%)	
occurrences (all)	29	46	
Chest pain			
subjects affected / exposed	9 / 239 (3.77%)	13 / 246 (5.28%)	
occurrences (all)	9	14	
Fatigue			
subjects affected / exposed	59 / 239 (24.69%)	48 / 246 (19.51%)	
occurrences (all)	70	61	
Oedema peripheral			
subjects affected / exposed	13 / 239 (5.44%)	11 / 246 (4.47%)	
occurrences (all)	16	14	
Pyrexia			
subjects affected / exposed	17 / 239 (7.11%)	25 / 246 (10.16%)	
occurrences (all)	17	26	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	18 / 239 (7.53%)	28 / 246 (11.38%)	
occurrences (all)	20	31	
Dyspnoea			

subjects affected / exposed	19 / 239 (7.95%)	31 / 246 (12.60%)	
occurrences (all)	20	35	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	29 / 239 (12.13%)	18 / 246 (7.32%)	
occurrences (all)	29	19	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	17 / 239 (7.11%)	15 / 246 (6.10%)	
occurrences (all)	21	20	
Aspartate aminotransferase increased			
subjects affected / exposed	14 / 239 (5.86%)	13 / 246 (5.28%)	
occurrences (all)	18	16	
Neutrophil count decreased			
subjects affected / exposed	50 / 239 (20.92%)	55 / 246 (22.36%)	
occurrences (all)	89	99	
Weight decreased			
subjects affected / exposed	11 / 239 (4.60%)	15 / 246 (6.10%)	
occurrences (all)	11	17	
White blood cell count decreased			
subjects affected / exposed	28 / 239 (11.72%)	26 / 246 (10.57%)	
occurrences (all)	50	47	
Platelet count decreased			
subjects affected / exposed	27 / 239 (11.30%)	24 / 246 (9.76%)	
occurrences (all)	41	32	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	32 / 239 (13.39%)	17 / 246 (6.91%)	
occurrences (all)	39	23	
Nervous system disorders			
Dizziness			
subjects affected / exposed	13 / 239 (5.44%)	22 / 246 (8.94%)	
occurrences (all)	15	23	
Headache			
subjects affected / exposed	18 / 239 (7.53%)	17 / 246 (6.91%)	
occurrences (all)	20	20	

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	86 / 239 (35.98%)	97 / 246 (39.43%)	
occurrences (all)	106	127	
Leukopenia			
subjects affected / exposed	13 / 239 (5.44%)	13 / 246 (5.28%)	
occurrences (all)	17	21	
Thrombocytopenia			
subjects affected / exposed	29 / 239 (12.13%)	31 / 246 (12.60%)	
occurrences (all)	46	53	
Neutropenia			
subjects affected / exposed	63 / 239 (26.36%)	72 / 246 (29.27%)	
occurrences (all)	91	136	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	12 / 239 (5.02%)	8 / 246 (3.25%)	
occurrences (all)	19	8	
Constipation			
subjects affected / exposed	58 / 239 (24.27%)	61 / 246 (24.80%)	
occurrences (all)	67	67	
Diarrhoea			
subjects affected / exposed	20 / 239 (8.37%)	37 / 246 (15.04%)	
occurrences (all)	24	46	
Nausea			
subjects affected / exposed	59 / 239 (24.69%)	61 / 246 (24.80%)	
occurrences (all)	66	73	
Vomiting			
subjects affected / exposed	21 / 239 (8.79%)	26 / 246 (10.57%)	
occurrences (all)	27	36	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	36 / 239 (15.06%)	28 / 246 (11.38%)	
occurrences (all)	44	33	
Alopecia			
subjects affected / exposed	62 / 239 (25.94%)	67 / 246 (27.24%)	
occurrences (all)	62	68	
Dry skin			

subjects affected / exposed	12 / 239 (5.02%)	6 / 246 (2.44%)	
occurrences (all)	13	6	
Pruritus			
subjects affected / exposed	66 / 239 (27.62%)	29 / 246 (11.79%)	
occurrences (all)	76	34	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	16 / 239 (6.69%)	17 / 246 (6.91%)	
occurrences (all)	16	19	
Hypothyroidism			
subjects affected / exposed	26 / 239 (10.88%)	21 / 246 (8.54%)	
occurrences (all)	26	27	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	20 / 239 (8.37%)	25 / 246 (10.16%)	
occurrences (all)	25	27	
Back pain			
subjects affected / exposed	17 / 239 (7.11%)	19 / 246 (7.72%)	
occurrences (all)	17	19	
Pain in extremity			
subjects affected / exposed	14 / 239 (5.86%)	9 / 246 (3.66%)	
occurrences (all)	17	9	
Infections and infestations			
COVID-19			
subjects affected / exposed	13 / 239 (5.44%)	17 / 246 (6.91%)	
occurrences (all)	13	17	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	58 / 239 (24.27%)	38 / 246 (15.45%)	
occurrences (all)	62	50	
Hypokalaemia			
subjects affected / exposed	11 / 239 (4.60%)	20 / 246 (8.13%)	
occurrences (all)	14	24	
Hypomagnesaemia			
subjects affected / exposed	14 / 239 (5.86%)	14 / 246 (5.69%)	
occurrences (all)	20	24	

Hyponatraemia subjects affected / exposed occurrences (all)	20 / 239 (8.37%) 24	14 / 246 (5.69%) 17	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 May 2020	The secondary efficacy objective endpoints were revised to clarify the definition of confirmed objective response and DOR and to measure TTCD in the participant's physical functioning and global health status. In addition to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0, the American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading scale will be used for reporting the severity of cytokine release syndrome (CRS). The study design was amended to include the requirement for participants to provide written informed consent at the time of initial radiographic disease progression per RECIST v1.1 if they met the criteria for treatment beyond radiographic disease progression and wished to continue study treatment. The protocol-specified adverse events of special interest (AESI) and serious adverse event (SAE) reporting period was extended until 90 days after the final dose of study treatment. Crossover will not be allowed from the control arm to the experimental arm. Exclusion criteria related to Epstein-Barr virus (EBV) infection and tests required at screening were clarified. Inclusion criteria were updated to clarify the coagulation criterion and include recommendations for oocyte cryopreservation and sperm conservation. Contraceptive language was added for female partners of childbearing potential. Tumor and response evaluation requirements were clarified: computerized tomography (CT) scans of the chest and abdomen with IV and oral contrast are required at screening and at subsequent tumor assessments; CT scan with contrast of the pelvis is required at screening; irradiated brain metastases do not need to be categorized and followed as target or nontarget lesions at baseline or at subsequent tumor assessments, untreated central nervous system (CNS) disease must be recorded as a non-target lesion per RECIST 1.1 at screening as well as at subsequent scheduled follow-up tumor assessments.
22 October 2020	The efficacy objectives were updated to reflect a focus on the primary population (PP) of participants without the presence or history of brain metastases at baseline. The study schema was updated to include the new study size of 470 participants and PP sample size of 400 participants, as well as a change in the approximate number of participants in each arm. The independent data monitoring committee (iDMC) review frequency was updated from approximately every 6 months to approximately every 4 to 6 months at the request of the iDMC. The end of the study was updated to indicate that it will occur when approximately 288 deaths have been observed in the PP. Also, the total length of study was updated to 50 months due to the updated statistical testing hierarchy and increased sample size. Exclusion criteria related to EBV infection and EBV tests required at screening were amended in alignment with other tiragolumab protocols. Patients positive for EBV VCA IgM or EBV PCR were not eligible. EBV VCA IgG or EBNA IgG test was required at screening to understand the infection history, but the results will not determine eligibility. The statistical analysis plan was updated to reflect the updated statistical testing hierarchy and sample size change. The primary analysis of PFS and the final analysis of OS was updated to occur approximately 24 months and 38 months after the first participant was randomized, respectively.
09 June 2021	The timing of the OS interim analysis and PFS primary analysis was updated to occur when approximately 202 OS events (51% of 400 patients) are observed in the PP. Immunosuppressive medications were removed from the prohibited therapy section and added to the cautionary therapy section to align with management guidelines that permit the use of immunosuppressive medications for the treatment of corticosteroid-refractory immune-mediated adverse events. The treatment interruption period for atezolizumab and tiragolumab/placebo was updated to 12 weeks after event onset instead of from last dose of study drug to align with all sections of the protocol.

15 November 2021	The term "intent-to-treat (ITT) population" was changed to "full analysis set" (FAS) and the term "primary population" (PP) was changed to "primary analysis set" (PAS). The method for computing the 95% CI of confirmed ORR was updated to the Wilson score method and the method for computing the 95% CI of the difference of confirmed ORR between treatment arms was updated to the Newcombe method to align with the calculation method specified in the study's Statistical Analysis Plan (SAP) version 1. It was clarified that the same information fraction in the PAS will be applied to calculate the statistical boundary in the FAS for the overall survival analyses.
20 December 2022	The adverse event management guidelines have been updated to align with the the Atezolizumab Investigator's Brochure. Immune-mediated hepatitis has been updated from a potential risk to an identified risk associated with tiragolumab. Lymphopenia has been updated to an identified risk associated with the combination of tiragolumab, atezolizumab, and chemotherapies. Embryofetal toxicity has been added as a potential risk associated with tiragolumab. The list of identified risks for atezolizumab has been revised to include myelitis, facial paresis and pericardial disorders. Hemophagocytic lymphohistiocytosis has been updated from a potential risk to an identified risk associated with atezolizumab. The list of adverse events of special interest has been revised to include myelitis and facial paresis. Text has been revised to indicate that caution should be used when considering atezolizumab for participants who have previously experienced a pericardial disorder while receiving another immunostimulatory anti-cancer agent. The association between anti-drug antibodies (ADAs) and infusion-related reactions (IRRs) to tiragolumab has been removed as a low incidence of ADAs against tiragolumab and no association between ADAs and IRRs have been observed to date. Language on study blinding has been amended to account for change in study treatment blinding status after the final overall survival analysis. Patient Reported Outcomes (PRO) assessments have been modified to remove the requirement for PRO Questionnaires for participants on active study treatment at the time of final OS analysis in order to reduce administrative burden to participants.
11 December 2023	The total duration of study participation for each individual was updated to approximately 72 months taking into account updated event projections. The survival follow-up duration was updated from 3 months to 6 months in response to continuing to follow ongoing patients in the study for limited information. The pharmacokinetic, immunogenicity, and biomarker sample collection schedule were changed so that samples are no longer collected at treatment discontinuation visit because the Sponsor has decided no additional sample collection was needed. At the time of Protocol Amendment version 7, all biomarker sample requirements were removed for remaining participants on study in order to reduce burden to participants.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported