Clinical trial results:
A Phase III, Open Label, Randomized Study of Atezolizumab (Anti-PD-L1 Antibody) Compared With a Platinum Agent (Cisplatin or Carboplatin) in Combination With Either Pemetrexed or Gemcitabine for PD-L1-Selected, Chemotherapy-Naive Patients With Stage IV Non-Squamous Or Squamous Non-Small Cell Lung Cancer

Summary

EudraCT number	2014-003083-21
Trial protocol	DE HU CZ ES GR FR PL IT
Global end of trial date	08 March 2022

Results information

Result version number	v2 (current)
This version publication date	05 March 2023
First version publication date	14 February 2021
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	GO29431

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02409342
WHO universal trial number (UTN)	-
Other trial identifiers	Other Sponsor ID: IMpower110

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

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

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

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to evaluate the safety and efficacy of atezolizumab compared with chemotherapy consisting of a platinum agent (cisplatin or carboplatin per investigator discretion) combined with either pemetrexed (non-squamous disease) or gemcitabine (squamous disease) in PD-L1-selected, chemotherapy-naïve patients with Stage IV Non-Small Cell Lung Cancer.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 July 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	34 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Brazil: 31
Country: Number of subjects enrolled	China: 3
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Spain: 35
Country: Number of subjects enrolled	France: 27
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	Greece: 32
Country: Number of subjects enrolled	Hungary: 26
Country: Number of subjects enrolled	Italy: 46
Country: Number of subjects enrolled	Japan: 51
Country: Number of subjects enrolled	Korea, Republic of: 11
Country: Number of subjects enrolled	Poland: 51
Country: Number of subjects enrolled	Romania: 54
Country: Number of subjects enrolled	Russian Federation: 50
Country: Number of subjects enrolled	Serbia: 42
Country: Number of subjects enrolled	Thailand: 14
Country: Number of subjects enrolled	Turkey: 36
Country: Number of subjects enrolled	Ukraine: 26

Country: Number of subjects enrolled	United States: 16
Worldwide total number of subjects	572
EEA total number of subjects	279

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)	289
From 65 to 84 years	281
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Recruitment included: Japan, Spain, Greece, Italy, Brazil, Russian, France, United States of America, Ukraine, Romania, Turkey, Poland, Serbia, Hungary, Thailand, Great Britain, Republic of Korea, Germany, China.

Pre-assignment

Screening details:

Only participants who are PD-L1-selected chemotherapy-naive with Stage IV non-small cell lung cancer (NSCLC) were enrolled.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Chemotherapy

Arm description:

Participants with non-squamous NSCLC will receive chemotherapy with pemetrexed in combination with either cisplatin or carboplatin (per investigator discretion) on Day 1 of each 21-day cycle for 4 or 6 cycles as per local standard of care, followed by maintenance therapy with pemetrexed alone as per local standard of care until disease progression (per RECIST v1.1), unacceptable toxicity, or death (maximum up to approximately 58 months). Participants with squamous NSCLC will receive chemotherapy with gemcitabine on Days 1 and 8 of each 21-day cycle in combination with either cisplatin or carboplatin on Day 1 of each 21-day cycle for 4 or 6 cycles as per local standard of care, followed by best supportive care as per local standard of care until disease progression, unacceptable toxicity, or death (maximum up to approximately 58 months).

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

Dosage and administration details:

Carboplatin will be administered as intravenous infusion at a dose of area under the concentration-time curve (AUC) 6 when given in combination with pemetrexed or at a dose of AUC 5 when given in combination with gemcitabine, every 21 days for 4 or 6 cycles as per local standard of care.

Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pemetrexed will be administered as intravenous infusion at a dose of 500 mg/m^2 on Day 1 of each 21-day cycle as per local standard of care until disease progression (per RECIST v1.1), unacceptable toxicity, or death (maximum up to approximately 58 months).

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine will be administered as intravenous infusion at a dose of 1250 mg/m^2 (in combination with cisplatin) or 1000 mg/m^2 (in combination with carboplatin), on Days 1 and 8 of each 21-day cycle for 4 or 6 cycles as per local standard of care.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cisplatin will be administered as intravenous infusion at a dose of 75 mg per meter squared (mg/m^2) every 21 days for 4 or 6 cycles as per local standard of care.

Arm title	Atezolizumab

Arm description:

Participants with squamous or non-squamous NSCLC will receive atezolizumab on Day 1 of each 21-day cycle until loss of clinical benefit (as assessed by the investigator), unacceptable toxicity, or death (maximum up to approximately 58 months).

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

Dosage and administration details:

Atezolizumab 1200 milligram (mg) will be administered as intravenous infusion every 21 days until loss of clinical benefit (as assessed by the investigator), unacceptable toxicity, or death (maximum up to approximately 58 months).

Number of subjects in period 1	Chemotherapy	Atezolizumab
Started	287	285
Completed	0	0
Not completed	287	285
Participant Moved Into Roll-Over Study	-	2
Consent withdrawn by subject	24	17
Local ethics requires subjects' data be removed.	-	1
Study Terminated By Sponsor	48	59
Death	211	201
Sponsor Decision	1	-
Lost to follow-up	3	5

Baseline characteristics

Reporting groups	
Reporting group title	Chemotherapy
Reporting group description:	
Participants with non-squamous NSCLC will receive chemotherapy with pemetrexed in combination with either cisplatin or carboplatin (per investigator discretion) on Day 1 of each 21-day cycle for 4 or 6 cycles as per local standard of care, followed by maintenance therapy with pemetrexed alone as per local standard of care until disease progression (per RECIST v1.1), unacceptable toxicity, or death (maximum up to approximately 58 months). Participants with squamous NSCLC will receive chemotherapy with gemcitabine on Days 1 and 8 of each 21-day cycle in combination with either cisplatin or carboplatin on Day 1 of each 21-day cycle for 4 or 6 cycles as per local standard of care, followed by best supportive care as per local standard of care until disease progression, unacceptable toxicity, or death (maximum up to approximately 58 months).	
Reporting group title	Atezolizumab
Reporting group description:	
Participants with squamous or non-squamous NSCLC will receive atezolizumab on Day 1 of each 21-day cycle until loss of clinical benefit (as assessed by the investigator), unacceptable toxicity, or death (maximum up to approximately 58 months).	

Reporting group values	Chemotherapy	Atezolizumab	Total
Number of subjects	287	285	572
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	140	149	289
From 65-84 years	145	136	281
85 years and over	2	0	2
Age Continuous Units: Years			
arithmetic mean	63.8	63.1	
standard deviation	± 8.8	± 8.8	-
Sex: Female, Male Units:			
Female	89	87	176
Male	198	198	396
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	33	48	81
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	2	4
White	247	232	479
More than one race	0	1	1
Unknown or Not Reported	5	2	7

Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	14	21	35
Not Hispanic or Latino	265	262	527
Unknown or Not Reported	8	2	10

End points

End points reporting groups

Reporting group title	Chemotherapy
Reporting group description:	
Participants with non-squamous NSCLC will receive chemotherapy with pemetrexed in combination with either cisplatin or carboplatin (per investigator discretion) on Day 1 of each 21-day cycle for 4 or 6 cycles as per local standard of care, followed by maintenance therapy with pemetrexed alone as per local standard of care until disease progression (per RECIST v1.1), unacceptable toxicity, or death (maximum up to approximately 58 months). Participants with squamous NSCLC will receive chemotherapy with gemcitabine on Days 1 and 8 of each 21-day cycle in combination with either cisplatin or carboplatin on Day 1 of each 21-day cycle for 4 or 6 cycles as per local standard of care, followed by best supportive care as per local standard of care until disease progression, unacceptable toxicity, or death (maximum up to approximately 58 months).	
Reporting group title	Atezolizumab
Reporting group description:	
Participants with squamous or non-squamous NSCLC will receive atezolizumab on Day 1 of each 21-day cycle until loss of clinical benefit (as assessed by the investigator), unacceptable toxicity, or death (maximum up to approximately 58 months).	
Subject analysis set title	Chemotherapy Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
Chemotherapy in the safety-evaluable participants.	
Subject analysis set title	Atezolizumab Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
Atezolizumab in the safety-evaluable participants.	

Primary: Overall Survival (OS) in the TC3 or IC3-WT Populations

End point title	Overall Survival (OS) in the TC3 or IC3-WT Populations
End point description:	
OS is defined as the time from randomization to death from any cause. Note: 999999=not estimable.	
End point type	Primary
End point timeframe:	
From randomization to death from any cause until data cut-off on 10 September 2018 (up to approximately 38 months)	

End point values	Chemotherapy	Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	107		
Units: Months				
median (confidence interval 95%)				
TC3 or IC3-WT Population	13.1 (7.4 to 16.5)	20.2 (16.5 to 999999)		

Statistical analyses

Statistical analysis title	OS Statistical Analysis
Statistical analysis description: TC3 or IC3-WT Population	
Comparison groups	Chemotherapy v Atezolizumab
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0106
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.595
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.398
upper limit	0.89

Notes:

[1] - Stratified analysis. OS was tested hierarchically in the efficacy analysis populations, first TC3 or IC3-WT then TC2/3 or IC2/3-WT and the TC1/2/3 or IC1/2/3-WT population.

Primary: Overall Survival (OS) in the TC2/3 or IC2/3-WT and TC1/2/3 or IC1/2/3-WT Populations

End point title	Overall Survival (OS) in the TC2/3 or IC2/3-WT and TC1/2/3 or IC1/2/3-WT Populations

End point description:

OS is defined as the time from randomization to death from any cause. Note: n=participants with data at given timepoint. 999999=not estimable.

End point type	Primary

End point timeframe:

From randomization to death from any cause until data cut-off on 4 February 2020 (up to approximately 54.5 months)

End point values	Chemotherapy	Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	277	277		
Units: Months				
median (confidence interval 95%)				
TC2/3 or IC2/3-WT Population (n=162, n=166)	16.1 (12.6 to 18.0)	19.9 (17.2 to 25.3)		
TC1/2/3 or IC1/2/3-WT Population (n=277, n=277)	14.7 (11.2 to 16.5)	18.9 (13.4 to 23.0)		

Statistical analyses

Statistical analysis title	OS Statistical Analysis
Statistical analysis description: TC1/2/3 or IC/1/2/3-WT	
Comparison groups	Chemotherapy v Atezolizumab

Number of subjects included in analysis	554
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.107 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.845
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.688
upper limit	1.037

Notes:

[2] - Stratified analysis. OS was tested hierarchically in the efficacy analysis populations.

[3] - P-value is descriptive as it was not formally tested.

Statistical analysis title	OS Statistical Analysis

Statistical analysis description:

TC2/3 or IC2/3-WT Population

Comparison groups	Chemotherapy v Atezolizumab
Number of subjects included in analysis	554
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.3091
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.868
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.661
upper limit	1.14

Notes:

[4] - Stratified analysis. OS was tested hierarchically in the efficacy analysis populations.

Secondary: Progression-free Survival (PFS) in the TC3 or IC3-WT Populations

End point title	Progression-free Survival (PFS) in the TC3 or IC3-WT Populations

End point description:

PFS is defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator with use of RECIST v1.1, or death from any cause, whichever occurs first.

End point type	Secondary

End point timeframe:

From randomization to the first occurrence of disease progression or death from any cause, whichever occurs first until data cut-off on 10 September 2018 (up to approximately 38 months)

End point values	Chemotherapy	Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	107		
Units: Months				
number (confidence interval 95%)				
TC3 or IC3-WT Population	5.0 (4.2 to 5.7)	8.1 (6.8 to 11.0)		

Statistical analyses

Statistical analysis title	PSF Statistical Analysis
Statistical analysis description: TC3 or IC3-WT Population	
Comparison groups	Chemotherapy v Atezolizumab
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.007 [6]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.449
upper limit	0.884

Notes:

[5] - Stratified Analysis

[6] - P-value is descriptive as it was not formally tested.

Secondary: Progression-free Survival (PFS) in the TC2/3 or IC2/3-WT and TC1/2/3 or IC1/2/3-WT Populations

End point title	Progression-free Survival (PFS) in the TC2/3 or IC2/3-WT and TC1/2/3 or IC1/2/3-WT Populations

End point description:

PFS is defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator with use of RECIST v1.1, or death from any cause, whichever occurs first. Note: n=participants with data at given timepoint.

End point type	Secondary

End point timeframe:

From randomization to the first occurrence of disease progression or death from any cause, whichever occurs first until data cut-off on 4 February 2020 (up to approximately 54.5 months)

End point values	Chemotherapy	Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	277	277		
Units: Months				
number (confidence interval 95%)				
TC2/3 or IC2/3-WT Population (n=162, n=166)	5.5 (4.5 to 5.7)	7.3 (5.6 to 9.3)		
TC1/2/3 or IC1/2/3-WT Population (n=277, n=277)	5.6 (4.7 to 5.7)	5.8 (5.5 to 7.3)		

Statistical analyses

Statistical analysis title	PFS Statistical Analysis
Statistical analysis description: TC1/2/3 or IC1/2/3-WT Population	
Comparison groups	Chemotherapy v Atezolizumab
Number of subjects included in analysis	554
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.0004 [8]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.716
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.595
upper limit	0.863

Notes:

[7] - Stratified Analysis

[8] - P-value is descriptive as it was not formally tested.

Statistical analysis title	PFS Statistical Analysis
Statistical analysis description: TC2/3 or IC2/3-WT Population	
Comparison groups	Chemotherapy v Atezolizumab
Number of subjects included in analysis	554
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.0004 [10]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.641
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.501
upper limit	0.82

Notes:

[9] - Stratified Analysis

[10] - P-value is descriptive as it was not formally tested.

Secondary: Percentage of Participants With Objective Response (ORR) in the TC3 or IC3-WT Populations

End point title	Percentage of Participants With Objective Response (ORR) in the TC3 or IC3-WT Populations

End point description:

Objective response (partial response plus complete response) as determined by the investigator according to RECIST v1.1.

End point type	Secondary

End point timeframe:

Every 6 weeks for 48 weeks following Day 1, thereafter every 9 weeks after completion of Week 48 tumor assessment, regardless of treatment delays, until radiographic disease progression until data cut-off on 10 Sep 2018 (up to approximately 38 months)

End point values	Chemotherapy	Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	107		
Units: Percentage of participants				
number (not applicable)				
TC3 or IC3-WT Population	28.6	38.3		

Statistical analyses

Statistical analysis title	ORR Statistical Analysis

Statistical analysis description:

TC3 or IC3-WT Population

Comparison groups	Chemotherapy v Atezolizumab
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority[11]
Parameter estimate	Difference in ORR
Point estimate	9.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.07
upper limit	23.56

Notes:

[11] - Stratified Analysis

Secondary: Percentage of Participants With Objective Response (ORR) in the TC2/3 or IC2/3-WT and TC1/2/3 or IC1/2/3-WT Populations

End point title	Percentage of Participants With Objective Response (ORR) in the TC2/3 or IC2/3-WT and TC1/2/3 or IC1/2/3-WT Populations

End point description:

Objective response (partial response plus complete response) as determined by the investigator according to RECIST v1.1. Note: n=participants with data at given timepoint.

End point type	Secondary

End point timeframe:

Every 6 weeks for 48 weeks following Day 1, thereafter every 9 weeks after completion of Week 48 tumor assessment, regardless of treatment delays, until radiographic disease progression until data cut-off on 4 Feb 2020 (up to approximately 54.5 months)

End point values	Chemotherapy	Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	277	277		
Units: Percentage of participants				
number (not applicable)				
TC2/3 or IC2/3-WT Population (n=162, n=166)	32.1	33.7		
TC1/2/3 or IC1/2/3-WT Population (n=277, n=277)	32.1	31.4		

Statistical analyses

Statistical analysis title	ORR Statistical Analysis

Statistical analysis description:

TC1/2/3 or IC1/2/3-WT Population

Comparison groups	Chemotherapy v Atezolizumab
Number of subjects included in analysis	554
Analysis specification	Pre-specified
Analysis type	superiority[12]
Parameter estimate	Difference in ORR
Point estimate	-0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.84
upper limit	7.39

Notes:

[12] - Stratified analysis

Statistical analysis title	ORR Statistical Analysis

Statistical analysis description:

TC2/3 or IC2/3-WT Population

Comparison groups	Chemotherapy v Atezolizumab

Number of subjects included in analysis	554
Analysis specification	Pre-specified
Analysis type	superiority[13]
Parameter estimate	Difference in ORR
Point estimate	1.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.14
upper limit	12.42

Notes:

[13] - Stratified analysis

Secondary: Duration of Response (DOR) in the TC3 or IC3-WT Populations

End point title	Duration of Response (DOR) in the TC3 or IC3-WT Populations

End point description:

DOR is defined as the time from the first occurrence of a documented objective response to the time of disease progression, as determined by the investigator with use of RECIST v1.1, or death from any cause, whichever occurs first. Note: 999999=not estimable

End point type	Secondary

End point timeframe:

From first occurrence of a complete response or partial response, whichever occurs first, until first date that progressive disease or death is documented, whichever occurs first until data cut-off on 10 September 2018 (up to approximately 38 months)

End point values	Chemotherapy	Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	41		
Units: Months				
number (confidence interval 95%)				
TC3 or IC3-WT Population	6.7 (5.5 to 17.3)	999999 (11.8 to 999999)		

Statistical analyses

Statistical analysis title	DOR Statistical Analysis

Statistical analysis description:

TC3 or IC3-WT Population

Comparison groups	Chemotherapy v Atezolizumab
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority[14]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.365

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.166
upper limit	0.8

Notes:

[14] - Stratified Analysis

Secondary: Duration of Response (DOR) in the TC2/3 or IC2/3-WT and TC1/2/3 or IC1/2/3-WT Populations

End point title	Duration of Response (DOR) in the TC2/3 or IC2/3-WT and TC1/2/3 or IC1/2/3-WT Populations

End point description:

DOR is defined as the time from the first occurrence of a documented objective response to the time of disease progression, as determined by the investigator with use of RECIST v1.1, or death from any cause, whichever occurs first. Note: n=participants with data at given timepoint. 999999=not estimable

End point type	Secondary

End point timeframe:

From first occurrence of a complete response or partial response, whichever occurs first, until first date that progressive disease or death is documented, whichever occurs first until data cut-off on 4 February 2020 (up to approximately 54.5 months)

End point values	Chemotherapy	Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	87		
Units: Months				
number (confidence interval 95%)				
TC2/3 or IC2/3-WT Population (n=52, n=56)	5.8 (5.1 to 9.8)	38.9 (16.9 to 999999)		
TC1/2/3 or IC1/2/3-WT Population (n=89, n=87)	5.7 (5.1 to 8.8)	26.3 (16.1 to 43.7)		

Statistical analyses

Statistical analysis title	DOR Statistical Analysis
Statistical analysis description:	
TC1/2/3 or IC1/2/3-WT Population	
Comparison groups	Chemotherapy v Atezolizumab
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority[15]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.284
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.19
upper limit	0.424

Notes:
[15] - Stratified analysis

Statistical analysis title	DOR Statistical Analysis
Statistical analysis description:	
TC2/3 or IC2/3-WT Population	
Comparison groups	Chemotherapy v Atezolizumab
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority[16]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.235
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.135
upper limit	0.409

Notes:
[16] - Stratified analysis

Secondary: Percentage of Participants Who are Alive at 1 and 2 Years in the TC3 or IC3-WT Populations

End point title	Percentage of Participants Who are Alive at 1 and 2 Years in the TC3 or IC3-WT Populations

End point description:

End point type	Secondary

End point timeframe:
Baseline to 2 years or death, whichever occurs first until data cut-off on 10 September 2018 (up to approximately 38 months)

End point values	Chemotherapy	Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	107		
Units: Percentage of participants				
number (confidence interval 95%)				
1-Year TC3 or IC3-WT (n=98; n=107)	50.64 (40.00 to 61.27)	64.90 (55.36 to 74.43)		
2-Year TC3 or IC3-WT (n=98; n=107)	24.79 (13.11 to 36.47)	45.49 (32.11 to 58.88)		

Statistical analyses

Statistical analysis title	% of Participants Alive Statistical Analysis

Statistical analysis description:
2-Year TC3 or IC3-WT Population

Comparison groups	Chemotherapy v Atezolizumab
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in Event Free Rate
Point estimate	20.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.94
upper limit	38.47

Statistical analysis title	% of Participants Alive Statistical Analysis
Statistical analysis description:	
1-Year TC3 or IC3-WT Population	
Comparison groups	Chemotherapy v Atezolizumab
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in Event Free Rate
Point estimate	14.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	28.55

Secondary: Percentage of Participants Who are Alive at 1 and 2 Years in the TC2/3 or IC2/3-WT Populations

End point title	Percentage of Participants Who are Alive at 1 and 2 Years in the TC2/3 or IC2/3-WT Populations
End point description:	
Note: n=participants with data at given timepoint.	
End point type	Secondary
End point timeframe:	
Baseline to 2 years or death, whichever occurs firstuntil clinical cut-off date on 4 February 2020 (up to approximately 54.5 months)	

End point values	Chemotherapy	Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162	166		
Units: Percentage of participants				
number (confidence interval 95%)				

1-Year TC2/3 or IC2/3-WT (n=162; n=166)	58.65 (50.95 to 66.35)	63.39 (56.00 to 70.77)		
2-Year TC2/3 or IC2/3-WT (n=162; n=166)	35.42 (27.91 to 42.94)	44.15 (36.51 to 51.80)		

Statistical analyses

Statistical analysis title	% of Participants Alive Statistical Analysis
Statistical analysis description:	
2-Year TC2/3 or IC2/3-WT Population	
Comparison groups	Chemotherapy v Atezolizumab
Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in Event Free Rate
Point estimate	8.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.99
upper limit	19.45

Statistical analysis title	% of Participants Alive Statistical Analysis
Statistical analysis description:	
1-Year TC2/3 or IC2/3-WT Population	
Comparison groups	Chemotherapy v Atezolizumab
Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in Event Free Rate
Point estimate	4.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.93
upper limit	15.4

Secondary: Percentage of Participants Who are Alive at 1 and 2 Years in the TC1/2/3 or IC1/2/3-WT Populations

End point title	Percentage of Participants Who are Alive at 1 and 2 Years in the TC1/2/3 or IC1/2/3-WT Populations
End point description:	
Note: n=participants with data at given timepoint.	
End point type	Secondary

End point timeframe:

Baseline to 2 years or death, whichever occurs firstuntil clinical cut-off date on 4 February 2020 (up to approximately 54.5 months)

End point values	Chemotherapy	Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	277	277		
Units: Percentage of participants				
number (confidence interval 95%)				
1-Year TC1/2/3 or IC1/2/3-WT (n=277; n=277)	54.89 (48.93 to 60.4)	59.95 (54.12 to 65.78)		
2-Year TC1/2/3 or IC1/2/3-WT (n=277; n=277)	30.82 (25.28 to 36.36)	41.76 (35.84 to 47.67)		

Statistical analyses

Statistical analysis title	% of Participants Alive Statistical Analysis
Statistical analysis description:	
2-Year TC1/2/3 or IC1/2/3-WT Population	
Comparison groups	Chemotherapy v Atezolizumab
Number of subjects included in analysis	554
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in Event Free Rate
Point estimate	10.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.83
upper limit	19.04

Statistical analysis title	% of Participants Alive Statistical Analysis
Statistical analysis description:	
1-Year TC1/2/3 or IC1/2/3-WT Population	
Comparison groups	Chemotherapy v Atezolizumab
Number of subjects included in analysis	554
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in Event Free Rate
Point estimate	5.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.27
upper limit	13.4

Secondary: Time to Deterioration (TTD) in Patient-reported Lung Cancer Symptoms Score as Assessed by the Symptoms in Lung Cancer (SILC) Scale Symptom Score in the TC3 or IC3-WT Populations

End point title	Time to Deterioration (TTD) in Patient-reported Lung Cancer Symptoms Score as Assessed by the Symptoms in Lung Cancer (SILC) Scale Symptom Score in the TC3 or IC3-WT Populations

End point description:

TTD in each of the patient-reported lung cancer symptoms with use of the SILC scale. The SILC scale is a nine-item content valid self-report measure of lung cancer symptoms. It measures severity of cough, dyspnea, and chest pain with a total symptom severity score. Each SILC symptom scale (dyspnea, cough, chest pain) score was calculated as the average of the component items (range 0 to 4). An increase in score suggested worsening in symptomatology. A symptom score change of 0.3 points for the dyspnea and cough scores was considered to be clinically significant; whereas a symptom score change of 0.5 points for the chest pain score was considered to be clinically significant.
Note: n=participants with data at given timepoint. 999999=not estimable.

End point type	Secondary

End point timeframe:

Baseline until data cut-off on 10 September 2018 (up to approximately 38 months)

End point values	Chemotherapy	Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	107		
Units: Months				
median (confidence interval 95%)				
Cough (n=98, n=107)	3.4 (1.3 to 12.4)	3.5 (1.0 to 10.8)		
Dyspnea (n=98, n=107)	1.0 (0.5 to 1.9)	1.3 (0.7 to 3.6)		
Chest pain (n=98, n=107)	1.1 (0.7 to 999999)	1.7 (0.7 to 4.5)		

Statistical analyses

Statistical analysis title	TTD Statistical Analysis
Statistical analysis description:	
Cough in TC3 or IC3-WT Populations	
Comparison groups	Chemotherapy v Atezolizumab
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority[17]
Parameter estimate	Hazard ratio (HR)
Point estimate	1.142
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.657
upper limit	1.984

Notes:
[17] - Stratified Analysis

Statistical analysis title	TTD Statistical Analysis
Statistical analysis description:	
Chest pain in TC3 or IC3-WT Populations	
Comparison groups	Chemotherapy v Atezolizumab
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority[18]
Parameter estimate	Hazard ratio (HR)
Point estimate	1.229
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.737
upper limit	2.049

Notes:
[18] - Stratified analysis

Statistical analysis title	TTD Statistical Analysis
Statistical analysis description:	
Dyspnoea in TC3 or IC3-WT Populations	
Comparison groups	Chemotherapy v Atezolizumab
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority[19]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.891
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.555
upper limit	1.43

Notes:
[19] - Stratified analysis

Secondary: Change From Baseline in Patient-reported Lung Cancer Symptoms Score as Assessed by the SILC Scale Symptom Score in the TC3 or IC3-WT Populations

End point title	Change From Baseline in Patient-reported Lung Cancer Symptoms Score as Assessed by the SILC Scale Symptom Score in the TC3 or IC3-WT Populations

End point description:
Change from baseline in each of the patient-reported lung cancer symptoms (cough, dyspnea, or chest pain) with use of the SILC scale. Note: n=participants with data at given timepoint. 9999=Not available; No participant analysed at given timepoint. 999999=not estimable.

End point type	Secondary

End point timeframe:
Baseline until data cut-off on 10 September 2018 (up to approximately 38 months)

End point values	Chemotherapy	Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	61		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Chest Pain, Week 1 (n=44, n=47)	0.57 (± 1.23)	0.31 (± 0.84)		
Chest Pain, Week 2 (n=42, n=48)	0.42 (± 1.13)	0.33 (± 0.85)		
Chest Pain, Week 3 (n=44, n=49)	0.25 (± 1.26)	0.43 (± 0.97)		
Chest Pain, Week 4 (n=41, n=49)	0.15 (± 1.21)	0.43 (± 1.08)		
Chest Pain, Week 5 (n=3*, n=47)	0.27 (± 1.19)	0.28 (± 1.00)		
Chest Pain, Week 6 (n=33, n=48)	0.30 (± 1.26)	0.25 (± 0.85)		
Chest Pain, Week 7 (n=30, n=44)	0.23 (± 1.04)	0.30 (± 0.97)		
Chest Pain, Week 8 (n=29, n=44)	0.17 (± 1.12)	0.20 (± 0.82)		
Chest Pain, Week 9 (n=31, n=47)	0.27 (± 1.00)	0.33 (± 1.07)		
Chest Pain, Week 10 (n=30, n=40)	0.30 (± 1.13)	0.25 (± 1.12)		
Chest Pain, Week 11 (n=29, n=34)	0.26 (± 1.32)	0.21 (± 0.96)		
Chest Pain, Week 12 (n=32, n=40)	0.22 (± 1.33)	0.33 (± 0.97)		
Chest Pain, Week 13 (n=28, n=38)	0.07 (± 1.17)	0.30 (± 1.04)		
Chest Pain, Week 14 (n=28, n=35)	0.07 (± 1.16)	0.27 (± 0.85)		
Chest Pain, Week 15 (n=30, n=40)	0.10 (± 1.23)	0.45 (± 1.01)		
Chest Pain, Week 16 (n=25, n=32)	0.00 (± 1.20)	0.19 (± 0.99)		
Chest Pain, Week 17 (n=27, n=34)	0.22 (± 1.41)	0.22 (± 1.20)		
Chest Pain, Week 18 (n=23, n=37)	0.11 (± 1.26)	0.26 (± 0.85)		
Chest Pain, Week 19 (n=22, n=32)	0.11 (± 1.01)	0.23 (± 0.94)		
Chest Pain, Week 20 (n=22, n=35)	0.20 (± 1.32)	0.23 (± 0.95)		
Chest Pain, Week 21 (n=18, n=36)	0.03 (± 0.83)	0.11 (± 0.87)		
Chest Pain, Week 22 (n=20, n=35)	0.30 (± 1.35)	0.19 (± 1.02)		
Chest Pain, Week 23 (n=16, n=33)	0.00 (± 1.00)	0.33 (± 0.84)		
Chest Pain, Week 24 (n=16, n=33)	-0.09 (± 0.88)	0.18 (± 1.13)		
Chest Pain, Week 25 (n=11, n=29)	0.27 (± 0.79)	0.29 (± 0.87)		
Chest Pain, Week 26 (n=13, n=32)	0.12 (± 1.31)	0.11 (± 0.72)		
Chest Pain, Week 27 (n=11, n=32)	0.05 (± 1.15)	0.20 (± 0.80)		
Chest Pain, Week 28 (n=11, n=30)	0.00 (± 0.81)	0.23 (± 0.98)		
Chest Pain, Week 29 (n=12, n=28)	-0.25 (± 0.87)	0.18 (± 0.80)		
Chest Pain, Week 30 (n=12, n=30)	0.21 (± 1.45)	0.32 (± 0.95)		
Chest Pain, Week 31 (n=11, n=29)	0.18 (± 1.72)	0.33 (± 0.90)		
Chest Pain, Week 32 (n=11, n=23)	0.41 (± 1.61)	0.35 (± 1.20)		
Chest Pain, Week 33 (n=13, n=26)	0.00 (± 1.44)	0.04 (± 1.03)		
Chest Pain, Week 34 (n=10, n=26)	0.40 (± 1.31)	0.31 (± 0.98)		
Chest Pain, Week 35 (n=11, n=27)	0.00 (± 1.16)	0.28 (± 1.13)		
Chest Pain, Week 36 (n=9, n=25)	0.06 (± 0.85)	0.08 (± 0.95)		
Chest Pain, Week 37 (n=8, n=23)	0.31 (± 1.25)	0.39 (± 0.89)		
Chest Pain, Week 38 (n=11, n=21)	0.23 (± 0.72)	0.31 (± 1.20)		
Chest Pain, Week 39 (n=9, n=22)	0.22 (± 1.00)	0.14 (± 0.92)		
Chest Pain, Week 40 (n=7, n=23)	0.43 (± 1.02)	0.30 (± 1.21)		
Chest Pain, Week 41 (n=7, n=20)	0.36 (± 1.07)	0.30 (± 1.01)		
Chest Pain, Week 42 (n=6, n=20)	0.25 (± 1.04)	0.33 (± 1.05)		
Chest Pain, Week 43 (n=5, n=20)	0.30 (± 1.15)	0.18 (± 1.29)		

Chest Pain, Week 44 (n=7, n=19)	0.14 (± 0.99)	0.42 (± 1.15)		
Chest Pain, Week 45 (n=4, n=21)	0.63 (± 0.48)	0.31 (± 0.90)		
Chest Pain, Week 46 (n=5, n=19)	0.30 (± 0.45)	0.37 (± 0.93)		
Chest Pain, Week 47 (n=4, n=18)	0.50 (± 0.71)	0.31 (± 0.86)		
Chest Pain, Week 48 (n=3, n=15)	0.50 (± 0.50)	0.17 (± 0.79)		
Chest Pain, Week 49 (n=3, n=17)	1.00 (± 1.32)	0.47 (± 1.07)		
Chest Pain, Week 50 (n=5, n=15)	0.80 (± 0.91)	0.20 (± 0.92)		
Chest Pain, Week 51 (n=4, n=16)	0.88 (± 0.85)	0.31 (± 0.89)		
Chest Pain, Week 52 (n=4, n=13)	0.75 (± 1.19)	0.54 (± 1.11)		
Chest Pain, Week 53 (n=5, n=12)	0.70 (± 0.84)	0.29 (± 1.08)		
Chest Pain, Week 54 (n=4, n=14)	1.13 (± 1.03)	0.25 (± 0.87)		
Chest Pain, Week 55 (n=3, n=13)	1.17 (± 1.26)	0.15 (± 0.99)		
Chest Pain, Week 56 (n=4, n=14)	0.38 (± 0.48)	0.29 (± 0.96)		
Chest Pain, Week 57 (n=3, n=13)	0.67 (± 0.58)	0.08 (± 0.73)		
Chest Pain, Week 58 (n=3, n=13)	1.17 (± 1.04)	0.19 (± 1.07)		
Chest Pain, Week 59 (n=3, n=9)	1.00 (± 0.87)	0.00 (± 0.87)		
Chest Pain, Week 60 (n=2, n=13)	0.50 (± 1.41)	0.38 (± 1.08)		
Chest Pain, Week 61 (n=3, n=14)	1.00 (± 0.87)	0.36 (± 1.12)		
Chest Pain, Week 62 (n=3, n=14)	0.83 (± 0.76)	0.43 (± 1.16)		
Chest Pain, Week 63 (n=2, n=12)	0.50 (± 0.71)	0.29 (± 0.86)		
Chest Pain, Week 64 (n=1, n=10)	0.00 (± 999999)	0.40 (± 1.22)		
Chest Pain, Week 65 (n=1, n=13)	0.00 (± 999999)	0.35 (± 1.11)		
Chest Pain, Week 66 (n=1, n=11)	0.00 (± 999999)	0.45 (± 1.44)		
Chest Pain, Week 67 (n=2, n=11)	1.00 (± 1.41)	-0.09 (± 0.80)		
Chest Pain, Week 68 (n=2, n=9)	0.75 (± 1.06)	0.39 (± 1.45)		
Chest Pain, Week 69 (n=2, n=10)	0.50 (± 0.71)	0.50 (± 1.33)		
Chest Pain, Week 70 (n=2, n=11)	1.00 (± 1.41)	0.18 (± 0.81)		
Chest Pain, Week 71 (n=2, n=10)	0.50 (± 0.71)	0.45 (± 1.32)		
Chest Pain, Week 72 (n=1, n=12)	1.00 (± 999999)	0.42 (± 1.18)		
Chest Pain, Week 73 (n=1, n=11)	1.50 (± 999999)	0.27 (± 1.19)		
Chest Pain, Week 74 (n=2, n=9)	0.50 (± 0.71)	0.50 (± 1.30)		
Chest Pain, Week 75 (n=2, n=9)	0.75 (± 1.06)	0.33 (± 1.32)		
Chest Pain, Week 76 (n=2, n=8)	0.50 (± 0.71)	0.00 (± 0.93)		
Chest Pain, Week 77 (n=2, n=8)	0.50 (± 0.71)	0.19 (± 1.33)		
Chest Pain, Week 78 (n=2, n=7)	1.00 (± 1.41)	0.21 (± 1.44)		
Chest Pain, Week 79 (n=2, n=8)	0.50 (± 0.71)	0.31 (± 1.31)		
Chest Pain, Week 80 (n=2, n=9)	0.75 (± 1.06)	0.72 (± 1.70)		
Chest Pain, Week 81 (n=2, n=6)	0.75 (± 1.06)	0.08 (± 1.72)		
Chest Pain, Week 82 (n=1, n=6)	0.00 (± 999999)	0.08 (± 1.24)		
Chest Pain, Week 83 (n=1, n=6)	0.00 (± 999999)	0.50 (± 1.48)		
Chest Pain, Week 84 (n=1, n=7)	0.50 (± 999999)	0.43 (± 1.43)		
Chest Pain, Week 85 (n=1, n=8)	0.00 (± 999999)	0.38 (± 1.41)		
Chest Pain, Week 86 (n=1, n=7)	0.00 (± 999999)	0.21 (± 1.44)		
Chest Pain, Week 87 (n=1, n=7)	0.00 (± 999999)	0.29 (± 1.41)		

Chest Pain, Week 88 (n=0, n=7)	9999 (± 9999)	0.43 (± 1.17)		
Chest Pain, Week 89 (n=0, n=5)	9999 (± 9999)	-0.20 (± 0.91)		
Chest Pain, Week 90 (n=0, n=7)	9999 (± 9999)	0.07 (± 1.13)		
Chest Pain, Week 91 (n=0, n=7)	9999 (± 9999)	-0.07 (± 0.89)		
Chest Pain, Week 92 (n=0, n=6)	9999 (± 9999)	0.33 (± 1.54)		
Chest Pain, Week 93 (n=0, n=7)	9999 (± 9999)	0.50 (± 1.47)		
Chest Pain, Week 94 (n=0, n=5)	9999 (± 9999)	0.20 (± 1.35)		
Chest Pain, Week 95 (n=0, n=6)	9999 (± 9999)	0.33 (± 1.54)		
Chest Pain, Week 96 (n=0, n=6)	9999 (± 9999)	0.33 (± 1.54)		
Chest Pain, Week 97 (n=0, n=7)	9999 (± 9999)	0.50 (± 1.47)		
Chest Pain, Week 98 (n=0, n=6)	9999 (± 9999)	0.33 (± 1.54)		
Chest Pain, Week 99 (n=0, n=4)	9999 (± 9999)	0.88 (± 1.18)		
Chest Pain, Week 100 (n=0, n=5)	9999 (± 9999)	0.50 (± 1.00)		
Chest Pain, Week 101 (n=0, n=6)	9999 (± 9999)	0.83 (± 0.93)		
Chest Pain, Week 102 (n=0, n=5)	9999 (± 9999)	0.50 (± 1.00)		
Chest Pain, Week 103 (n=0, n=4)	9999 (± 9999)	0.63 (± 1.11)		
Chest Pain, Week 104 (n=0, n=3)	9999 (± 9999)	1.00 (± 1.00)		
Chest Pain, Week 105 (n=0, n=3)	9999 (± 9999)	1.00 (± 1.00)		
Chest Pain, Week 106 (n=0, n=2)	9999 (± 9999)	0.50 (± 0.71)		
Chest Pain, Week 107 (n=0, n=3)	9999 (± 9999)	1.00 (± 1.00)		
Chest Pain, Week 108 (n=0, n=2)	9999 (± 9999)	1.50 (± 0.71)		
Chest Pain, Week 109 (n=0, n=2)	9999 (± 9999)	1.75 (± 1.06)		
Chest Pain, Week 110 (n=0, n=2)	9999 (± 9999)	2.00 (± 1.41)		
Chest Pain, Week 111 (n=0, n=2)	9999 (± 9999)	1.50 (± 0.71)		
Chest Pain, Week 112 (n=0, n=2)	9999 (± 9999)	1.50 (± 0.71)		
Chest Pain, Week 113 (n=0, n=2)	9999 (± 9999)	1.50 (± 0.71)		
Chest Pain, Week 114 (n=0, n=2)	9999 (± 9999)	2.00 (± 1.41)		
Chest Pain, Week 115 (n=0, n=2)	9999 (± 9999)	1.75 (± 1.06)		
Chest Pain, Week 116 (n=0, n=2)	9999 (± 9999)	2.00 (± 1.41)		
Chest Pain, Week 117 (n=0, n=2)	9999 (± 9999)	2.00 (± 1.41)		
Chest Pain, Week 118 (n=0, n=2)	9999 (± 9999)	2.00 (± 1.41)		
Chest Pain, Week 119 (n=0, n=2)	9999 (± 9999)	1.75 (± 1.06)		
Chest Pain, Week 120 (n=0, n=1)	9999 (± 9999)	2.50 (± 999999)		
Chest Pain, Week 121 (n=0, n=1)	9999 (± 9999)	2.00 (± 999999)		
Chest Pain, Week 122 (n=0, n=1)	9999 (± 9999)	3.00 (± 999999)		
Chest Pain, Week 123 (n=0, n=1)	9999 (± 9999)	2.50 (± 999999)		
Chest Pain, Week 124 (n=0, n=1)	9999 (± 9999)	3.00 (± 999999)		
Chest Pain, Week 125 (n=0, n=1)	9999 (± 9999)	3.00 (± 999999)		
Chest Pain, Week 126 (n=0, n=1)	9999 (± 9999)	3.00 (± 999999)		
Chest Pain, Week 127 (n=0, n=1)	9999 (± 9999)	2.00 (± 999999)		
Chest Pain, Week 128 (n=0, n=1)	9999 (± 9999)	3.00 (± 999999)		
Chest Pain, Week 129 (n=0, n=1)	9999 (± 9999)	3.00 (± 999999)		
Chest Pain, Week 130 (n=0, n=1)	9999 (± 9999)	2.00 (± 999999)		
Chest Pain, Week 131 (n=0, n=1)	9999 (± 9999)	2.00 (± 999999)		

Cough, Week 1 (n=44, n=47)	0.13 (± 0.86)	0.10 (± 0.70)		
Cough, Week 2 (n=42, n=48)	-0.01 (± 0.99)	0.19 (± 0.75)		
Cough, Week 3 (n=44, n=49)	-0.03 (± 0.76)	-0.01 (± 0.76)		
Cough, Week 4 (n=41, n=49)	-0.02 (± 1.02)	-0.03 (± 0.98)		
Cough, Week 5 (n=39, n=47)	-0.01 (± 0.84)	0.00 (± 0.96)		
Cough, Week 6 (n=33, n=48)	-0.18 (± 0.93)	-0.18 (± 0.89)		
Cough, Week 7 (n=30, n=44)	-0.20 (± 0.92)	-0.06 (± 0.98)		
Cough, Week 8(n=29, n=44)	-0.10 (± 0.90)	-0.13 (± 0.91)		
Cough, Week 9(n=31, n=47)	-0.24 (± 0.86)	-0.06 (± 1.01)		
Cough, Week 10(n=30, n=40)	-0.07 (± 1.12)	-0.10 (± 1.02)		
Cough, Week 11(n=29, n=34)	0.02 (± 1.24)	-0.07 (± 1.07)		
Cough, Week 12(n=32, n=40)	-0.08 (± 1.30)	-0.09 (± 0.97)		
Cough, Week 13(n=28, n=38)	-0.09 (± 1.22)	-0.20 (± 0.93)		
Cough, Week 14(n=28, n=35)	-0.20 (± 1.19)	-0.07 (± 0.95)		
Cough, Week 15(n=30, n=40)	-0.05 (± 1.35)	-0.19 (± 1.04)		
Cough, Week 16(n=25, n=32)	-0.10 (± 1.06)	-0.19 (± 0.94)		
Cough, Week 17(n=27, n=34)	-0.04 (± 0.99)	-0.21 (± 1.09)		
Cough, Week 18(n=23, n=37)	0.02 (± 1.23)	-0.26 (± 0.93)		
Cough, Week 19(n=22, n=32)	-0.23 (± 1.29)	-0.27 (± 0.87)		
Cough, Week 20 (n=22, n=35)	0.00 (± 1.33)	-0.33 (± 0.95)		
Cough, Week 21(n=18, n=36)	-0.17 (± 1.40)	-0.19 (± 0.88)		
Cough, Week 22(n=20, n=35)	-0.20 (± 1.32)	-0.17 (± 0.89)		
Cough, Week 23(n=16, n=33)	-0.22 (± 1.18)	0.05 (± 0.90)		
Cough, Week 24(n=16, n=33)	-0.13 (± 1.51)	-0.12 (± 0.80)		
Cough, Week 25(n=11, n=29)	-0.45 (± 0.96)	0.14 (± 0.82)		
Cough, Week 26(n=13, n=32)	-0.46 (± 1.20)	-0.03 (± 0.89)		
Cough, Week 27(n=11, n=32)	-0.50 (± 1.22)	-0.05 (± 0.94)		
Cough, Week 28(n=11, n=30)	-0.45 (± 0.88)	0.08 (± 0.84)		
Cough, Week 29(n=12, n=28)	-0.50 (± 1.31)	0.05 (± 0.67)		
Cough, Week 30(n=12, n=30)	-0.88 (± 1.13)	0.12 (± 0.88)		
Cough, Week 31(n=11, n=29)	-0.86 (± 1.40)	0.05 (± 0.74)		
Cough, Week 32(n=11, n=23)	-0.73 (± 1.56)	-0.04 (± 1.04)		
Cough, Week 33(n=13, n=26)	-0.77 (± 1.13)	-0.29 (± 1.06)		
Cough, Week 34(n=10, n=26)	-0.80 (± 1.18)	-0.02 (± 0.75)		
Cough, Week 35(n=11, n=27)	-0.14 (± 0.95)	-0.09 (± 1.10)		
Cough, Week 36(n=9, n=25)	-0.17 (± 0.66)	-0.36 (± 1.16)		
Cough, Week 37(n=8, n=23)	-0.25 (± 0.89)	-0.04 (± 0.84)		
Cough, Week 38(n=11, n=21)	0.05 (± 0.88)	-0.07 (± 1.11)		
Cough, Week 39(n=9, n=22)	-0.50 (± 0.90)	-0.20 (± 0.97)		
Cough, Week 40(n=7, n=23)	-0.36 (± 0.94)	-0.39 (± 1.23)		
Cough, Week 41(n=7, n=20)	0.21 (± 0.57)	0.05 (± 0.84)		
Cough, Week 42(n=6, n=20)	0.17 (± 0.52)	-0.20 (± 1.16)		
Cough, Week 43(n=5, n=20)	0.10 (± 0.55)	0.03 (± 1.06)		
Cough, Week 44(n=7, n=19)	0.36 (± 0.94)	-0.11 (± 1.09)		
Cough, Week 45(n=4, n=21)	0.25 (± 0.50)	-0.26 (± 0.92)		
Cough, Week 46(n=5, n=19)	0.10 (± 0.96)	0.08 (± 0.85)		
Cough, Week 47(n=4, n=18)	0.50 (± 0.58)	-0.03 (± 0.90)		
Cough, Week 48(n=3, n=15)	0.17 (± 0.29)	0.23 (± 0.68)		
Cough, Week 49(n=3, n=17)	0.67 (± 0.76)	0.26 (± 0.85)		
Cough, Week 50(n=5, n=15)	0.30 (± 0.76)	0.00 (± 0.85)		
Cough, Week 51(n=4, n=16)	0.13 (± 0.63)	0.06 (± 0.93)		
Cough, Week 52(n=4, n=13)	0.63 (± 0.95)	0.27 (± 0.97)		

Cough, Week 53(n=5, n=12)	0.70 (± 0.76)	0.38 (± 0.71)		
Cough, Week 54(n=4, n=14)	0.50 (± 0.41)	0.07 (± 0.70)		
Cough, Week 55(n=3, n=13)	0.67 (± 0.29)	0.12 (± 0.94)		
Cough, Week 56(n=4, n=14)	0.50 (± 0.41)	0.14 (± 0.97)		
Cough, Week 57(n=3, n=13)	0.50 (± 0.50)	0.15 (± 0.66)		
Cough, Week 58(n=3, n=13)	0.67 (± 0.29)	0.08 (± 1.00)		
Cough, Week 59(n=3, n=9)	0.33 (± 0.58)	0.06 (± 0.63)		
Cough, Week 60(n=2, n=13)	0.75 (± 0.35)	-0.04 (± 0.83)		
Cough, Week 61(n=3, n=14)	0.50 (± 0.50)	0.00 (± 0.88)		
Cough, Week 62(n=3, n=14)	0.33 (± 0.58)	0.14 (± 0.79)		
Cough, Week 63(n=2, n=12)	0.00 (± 0.00)	-0.04 (± 0.86)		
Cough, Week 64(n=1, n=10)	0.00 (± 999999)	0.35 (± 1.00)		
Cough, Week 65(n=1, n=13)	0.50 (± 999999)	0.12 (± 0.92)		
Cough, Week 66(n=1, n=11)	0.00 (± 999999)	0.45 (± 1.21)		
Cough, Week 67(n=2, n=11)	0.25 (± 0.35)	-0.09 (± 0.66)		
Cough, Week 68(n=2, n=9)	0.25 (± 0.35)	0.61 (± 1.29)		
Cough, Week 69(n=2, n=10)	0.25 (± 0.35)	0.50 (± 1.18)		
Cough, Week 70(n=2, n=11)	0.25 (± 0.35)	0.23 (± 0.79)		
Cough, Week 71(n=2, n=10)	0.00 (± 0.00)	0.55 (± 0.90)		
Cough, Week 72(n=1, n=12)	-0.50 (± 999999)	0.42 (± 0.93)		
Cough, Week 73(n=1, n=11)	0.00 (± 999999)	0.64 (± 1.07)		
Cough, Week 74(n=2, n=9)	0.00 (± 0.00)	0.56 (± 1.04)		
Cough, Week 75(n=2, n=9)	0.00 (± 0.71)	0.67 (± 1.35)		
Cough, Week 76(n=2, n=8)	0.25 (± 0.35)	0.31 (± 1.00)		
Cough, Week 77(n=2, n=8)	0.00 (± 0.00)	0.56 (± 1.15)		
Cough, Week 78(n=2, n=7)	0.25 (± 0.35)	0.36 (± 1.03)		
Cough, Week 79(n=2, n=8)	0.00 (± 0.00)	0.63 (± 1.19)		
Cough, Week 80(n=2, n=9)	0.25 (± 0.35)	0.33 (± 0.90)		
Cough, Week 81(n=2, n=6)	0.25 (± 0.35)	0.58 (± 1.28)		
Cough, Week 82(n=1, n=6)	0.00 (± 999999)	0.25 (± 1.08)		
Cough, Week 83(n=1, n=6)	0.00 (± 999999)	0.67 (± 1.21)		
Cough, Week 84(n=1, n=7)	0.50 (± 999999)	0.29 (± 0.95)		
Cough, Week 85(n=1, n=8)	0.00 (± 999999)	0.38 (± 1.03)		
Cough, Week 86(n=1, n=7)	0.00 (± 999999)	0.57 (± 1.24)		
Cough, Week 87(n=1, n=7)	0.00 (± 999999)	0.64 (± 1.35)		
Cough, Week 88(n=0, n=7)	9999 (± 9999)	0.64 (± 1.14)		
Cough, Week 89 (n=0, n=5)	9999 (± 9999)	0.50 (± 1.32)		
Cough, Week 90(n=0, n=7)	9999 (± 9999)	0.43 (± 1.10)		
Cough, Week 91(n=0, n=7)	9999 (± 9999)	0.50 (± 1.19)		
Cough, Week 92(n=0, n=6)	9999 (± 9999)	0.67 (± 1.21)		
Cough, Week 93(n=0, n=7)	9999 (± 9999)	0.79 (± 1.38)		
Cough, Week 94(n=0, n=5)	9999 (± 9999)	0.30 (± 0.97)		
Cough, Week 95(n=0, n=6)	9999 (± 9999)	0.67 (± 1.25)		
Cough, Week 96(n=0, n=6)	9999 (± 9999)	0.58 (± 1.20)		

Cough, Week 97(n=0, n=7)	9999 (± 9999)	0.57 (± 1.13)		
Cough, Week 98(n=0, n=6)	9999 (± 9999)	0.67 (± 1.25)		
Cough, Week 99(n=0, n=4)	9999 (± 9999)	0.25 (± 0.96)		
Cough, Week 100(n=0, n=5)	9999 (± 9999)	0.60 (± 1.14)		
Cough, Week 101(n=0, n=6)	9999 (± 9999)	0.50 (± 1.05)		
Cough, Week 102(n=0, n=5)	9999 (± 9999)	0.50 (± 1.00)		
Cough, Week 103(n=0, n=4)	9999 (± 9999)	0.25 (± 0.96)		
Cough, Week 104(n=0, n=3)	9999 (± 9999)	0.00 (± 1.00)		
Cough, Week 105(n=0, n=3)	9999 (± 9999)	0.33 (± 1.53)		
Cough, Week 106(n=0, n=2)	9999 (± 9999)	-0.50 (± 0.71)		
Cough, Week 107(n=0, n=3)	9999 (± 9999)	0.00 (± 1.00)		
Cough, Week 108(n=0, n=2)	9999 (± 9999)	0.00 (± 1.41)		
Cough, Week 109(n=0, n=2)	9999 (± 9999)	0.50 (± 2.12)		
Cough, Week 110(n=0, n=2)	9999 (± 9999)	0.50 (± 2.12)		
Cough, Week 111(n=0, n=2)	9999 (± 9999)	0.50 (± 2.12)		
Cough, Week 112(n=0, n=2)	9999 (± 9999)	0.00 (± 1.41)		
Cough, Week 113(n=0, n=2)	9999 (± 9999)	0.50 (± 2.12)		
Cough, Week 114(n=0, n=2)	9999 (± 9999)	0.50 (± 2.12)		
Cough, Week 115(n=0, n=2)	9999 (± 9999)	0.50 (± 2.12)		
Cough, Week 116(n=0, n=2)	9999 (± 9999)	0.50 (± 2.12)		
Cough, Week 117(n=0, n=2)	9999 (± 9999)	0.50 (± 2.12)		
Cough, Week 118(n=0, n=2)	9999 (± 9999)	0.50 (± 2.12)		
Cough, Week 119(n=0, n=2)	9999 (± 9999)	0.50 (± 2.12)		
Cough, Week 120(n=0, n=1)	9999 (± 9999)	2.00 (± 999999)		
Cough, Week 121(n=0, n=1)	9999 (± 9999)	2.00 (± 999999)		
Cough, Week 122(n=0, n=)	9999 (± 9999)	2.00 (± 999999)		
Cough, Week 123(n=0, n=1)	9999 (± 9999)	2.00 (± 999999)		
Cough, Week 124(n=0, n=1)	9999 (± 9999)	2.00 (± 999999)		
Cough, Week 125(n=0, n=1)	9999 (± 9999)	2.00 (± 999999)		
Cough, Week 126(n=0, n=1)	9999 (± 9999)	2.00 (± 999999)		
Cough, Week 127(n=0, n=1)	9999 (± 9999)	2.00 (± 999999)		
Cough, Week 128(n=0, n=1)	9999 (± 9999)	2.00 (± 999999)		
Cough, Week 129(n=0, n=1)	9999 (± 9999)	2.00 (± 999999)		
Cough, Week 130(n=0, n=1)	9999 (± 9999)	2.00 (± 999999)		
Cough, Week 131(n=0, n=1)	9999 (± 9999)	2.00 (± 999999)		
Dyspnoea, Week 1(n=44, n=47)	0.42 (± 0.81)	0.12 (± 0.76)		
Dyspnoea, Week 2(n=42, n=48)	0.33 (± 0.73)	0.29 (± 0.87)		
Dyspnoea, Week 3(n=44, n=49)	0.25 (± 0.75)	0.25 (± 0.97)		
Dyspnoea, Week 4(n=41, n=49)	0.43 (± 0.87)	0.28 (± 0.89)		
Dyspnoea, Week 5(n=39, n=47)	0.55 (± 0.81)	0.21 (± 1.00)		
Dyspnoea, Week 6(n=33, n=48)	0.50 (± 0.68)	0.21 (± 0.95)		
Dyspnoea, Week 7(n=30, n=44)	0.63 (± 0.74)	0.32 (± 1.08)		
Dyspnoea, Week 8(n=29, n=44)	0.50 (± 0.64)	0.25 (± 1.00)		
Dyspnoea, Week 9(n=31, n=47)	0.46 (± 0.86)	0.34 (± 1.01)		

Dyspnoea, Week 10(n=30, n=40)	0.43 (± 0.80)	0.49 (± 1.12)		
Dyspnoea, Week 11 (n=29, n=34)	0.36 (± 0.77)	0.24 (± 0.97)		
Dyspnoea, Week 12 (n=32, n=40)	0.39 (± 0.82)	0.35 (± 1.04)		
Dyspnoea, Week 13 (n=28, n=38)	0.43 (± 0.83)	0.23 (± 0.94)		
Dyspnoea, Week 14 (n=28, n=35)	0.26 (± 0.88)	0.26 (± 1.14)		
Dyspnoea, Week 15 (n=30, n=40)	0.36 (± 1.07)	0.39 (± 1.22)		
Dyspnoea, Week 16 (n=25, n=32)	0.18 (± 0.82)	0.26 (± 1.13)		
Dyspnoea, Week 17 (n=27, n=34)	0.48 (± 0.87)	0.16 (± 1.17)		
Dyspnoea, Week 18 (n=23, n=37)	0.39 (± 0.65)	0.21 (± 1.05)		
Dyspnoea, Week 19 (n=22, n=32)	0.29 (± 0.86)	0.33 (± 1.12)		
Dyspnoea, Week 20 (n=22, n=35)	0.60 (± 0.87)	0.23 (± 1.00)		
Dyspnoea, Week 21 (n=18, n=36)	0.27 (± 0.69)	0.40 (± 0.93)		
Dyspnoea, Week 22 (n=20, n=35)	0.55 (± 0.92)	0.22 (± 0.99)		
Dyspnoea, Week 23 (n=16, n=33)	0.34 (± 0.69)	0.38 (± 0.98)		
Dyspnoea, Week 24 (n=16, n=33)	0.36 (± 1.02)	0.42 (± 1.06)		
Dyspnoea, Week 25 (n=11, n=29)	0.22 (± 0.46)	0.50 (± 1.14)		
Dyspnoea, Week 26 (n=13, n=32)	0.32 (± 0.82)	0.28 (± 0.95)		
Dyspnoea, Week 27 (n=11, n=32)	0.35 (± 1.07)	0.37 (± 1.04)		
Dyspnoea, Week 28 (n=11, n=30)	0.35 (± 0.92)	0.45 (± 0.83)		
Dyspnoea, Week 29 (n=12, n=28)	0.20 (± 0.89)	0.38 (± 0.85)		
Dyspnoea, Week 30 (n=12, n=30)	0.18 (± 0.96)	0.54 (± 1.01)		
Dyspnoea, Week 31 (n=11, n=29)	0.18 (± 0.84)	0.41 (± 0.86)		
Dyspnoea, Week 32 (n=11, n=23)	0.22 (± 1.00)	0.58 (± 1.04)		
Dyspnoea, Week 33 (n=13, n=26)	0.20 (± 0.78)	0.36 (± 0.96)		
Dyspnoea, Week 34 (n=10, n=26)	0.16 (± 0.79)	0.28 (± 1.00)		
Dyspnoea, Week 35 (n=11, n=27)	0.11 (± 0.58)	0.27 (± 1.02)		
Dyspnoea, Week 36 (n=9, n=25)	0.11 (± 0.86)	-0.02 (± 1.04)		
Dyspnoea, Week 37 (n=8, n=23)	0.28 (± 0.63)	0.42 (± 1.13)		
Dyspnoea, Week 38 (n=11, n=21)	0.40 (± 0.76)	0.50 (± 1.25)		
Dyspnoea, Week 39 (n=9, n=22)	0.27 (± 0.81)	0.25 (± 0.86)		
Dyspnoea, Week 40 (n=7, n=23)	0.57 (± 0.76)	0.44 (± 1.13)		
Dyspnoea, Week 41 (n=7, n=20)	0.31 (± 0.58)	0.53 (± 1.17)		
Dyspnoea, Week 42 (n=6, n=20)	0.30 (± 0.55)	0.52 (± 1.07)		
Dyspnoea, Week 43 (n=5, n=20)	0.40 (± 0.57)	0.41 (± 1.18)		
Dyspnoea, Week 44 (n=7, n=19)	0.49 (± 0.60)	0.31 (± 1.14)		
Dyspnoea, Week 45 (n=4, n=21)	0.65 (± 0.38)	0.53 (± 1.04)		
Dyspnoea, Week 46 (n=5, n=19)	0.56 (± 0.71)	0.37 (± 0.97)		
Dyspnoea, Week 47 (n=4, n=18)	0.30 (± 0.68)	0.39 (± 0.92)		
Dyspnoea, Week 48 (n=3, n=15)	0.60 (± 0.72)	0.39 (± 0.93)		
Dyspnoea, Week 49 (n=3, n=17)	1.40 (± 1.20)	0.47 (± 0.76)		
Dyspnoea, Week 50 (n=5, n=15)	0.24 (± 0.59)	0.53 (± 0.96)		
Dyspnoea, Week 51 (n=4, n=16)	1.05 (± 1.02)	0.59 (± 1.02)		
Dyspnoea, Week 52 (n=4, n=13)	1.10 (± 1.01)	0.72 (± 1.20)		
Dyspnoea, Week 53 (n=5, n=12)	0.76 (± 1.28)	0.40 (± 1.01)		
Dyspnoea, Week 54 (n=4, n=14)	1.10 (± 1.16)	0.63 (± 1.02)		
Dyspnoea, Week 55 (n=3, n=13)	1.00 (± 0.53)	0.72 (± 1.13)		
Dyspnoea, Week 56 (n=4, n=14)	0.40 (± 0.86)	0.61 (± 1.07)		
Dyspnoea, Week 57 (n=3, n=13)	0.53 (± 0.61)	0.45 (± 1.02)		
Dyspnoea, Week 58 (n=3, n=13)	0.80 (± 0.53)	0.60 (± 1.20)		
Dyspnoea, Week 59 (n=3, n=9)	0.60 (± 0.72)	0.18 (± 1.08)		
Dyspnoea, Week 60 (n=2, n=13)	1.20 (± 1.13)	0.57 (± 0.89)		
Dyspnoea, Week 61 (n=3, n=14)	0.73 (± 0.76)	0.54 (± 1.00)		

Dyspnoea, Week 62 (n=3, n=14)	0.67 (± 0.83)	0.66 (± 1.11)		
Dyspnoea, Week 63 (n=2, n=12)	0.30 (± 0.42)	0.77 (± 0.80)		
Dyspnoea, Week 64 (n=1, n=10)	0.20 (± 999999)	0.66 (± 1.07)		
Dyspnoea, Week 65 (n=1, n=13)	0.60 (± 999999)	0.94 (± 1.28)		
Dyspnoea, Week 66 (n=1, n=11)	0.40 (± 999999)	0.67 (± 1.31)		
Dyspnoea, Week 67 (n=2, n=11)	0.50 (± 0.14)	0.33 (± 0.87)		
Dyspnoea, Week 68 (n=2, n=9)	0.20 (± 0.28)	0.82 (± 1.56)		
Dyspnoea, Week 69 (n=2, n=10)	0.30 (± 0.42)	0.74 (± 1.11)		
Dyspnoea, Week 70 (n=2, n=11)	0.30 (± 0.42)	0.75 (± 1.16)		
Dyspnoea, Week 71 (n=2, n=10)	0.10 (± 0.14)	0.84 (± 1.19)		
Dyspnoea, Week 72 (n=1, n=12)	0.00 (± 999999)	0.80 (± 1.09)		
Dyspnoea, Week 73 (n=1, n=11)	0.00 (± 999999)	0.67 (± 1.11)		
Dyspnoea, Week 74 (n=2, n=9)	0.20 (± 0.28)	0.89 (± 1.35)		
Dyspnoea, Week 75 (n=2, n=9)	0.30 (± 0.42)	0.71 (± 1.31)		
Dyspnoea, Week 76 (n=1, n=8)	0.30 (± 0.42)	0.53 (± 1.05)		
Dyspnoea, Week 77 (n=2, n=8)	0.40 (± 0.57)	0.65 (± 1.55)		
Dyspnoea, Week 78 (n=2, n=7)	0.30 (± 0.14)	0.40 (± 1.11)		
Dyspnoea, Week 79 (n=2, n=8)	0.10 (± 0.14)	0.55 (± 1.25)		
Dyspnoea, Week 80 (n=2, n=9)	0.50 (± 0.71)	0.69 (± 1.43)		
Dyspnoea, Week 81 (n=2, n=6)	0.40 (± 0.57)	0.53 (± 1.53)		
Dyspnoea, Week 82 (n=1, n=6)	0.60 (± 999999)	0.53 (± 1.09)		
Dyspnoea, Week 83 (n=1, n=6)	0.60 (± 999999)	0.87 (± 1.28)		
Dyspnoea, Week 84 (n=1, n=7)	0.80 (± 999999)	0.89 (± 1.13)		
Dyspnoea, Week 85 (n=1, n=8)	0.60 (± 999999)	0.83 (± 1.27)		
Dyspnoea, Week 86 (n=1, n=7)	0.40 (± 999999)	0.66 (± 1.33)		
Dyspnoea, Week 87 (n=1, n=7)	0.40 (± 999999)	0.66 (± 1.23)		
Dyspnoea, Week 88 (n=0, n=7)	9999 (± 9999)	1.20 (± 1.43)		
Dyspnoea, Week 89 (n=5, n=5)	9999 (± 9999)	0.56 (± 1.05)		
Dyspnoea, Week 90 (n=0, n=7)	9999 (± 9999)	0.74 (± 1.38)		
Dyspnoea, Week 91 (n=0, n=7)	9999 (± 9999)	0.51 (± 1.00)		
Dyspnoea, Week 92 (n=0, n=6)	9999 (± 9999)	0.87 (± 1.26)		
Dyspnoea, Week 93 (n=0, n=7)	9999 (± 9999)	1.20 (± 1.39)		
Dyspnoea, Week 94 (n=0, n=5)	9999 (± 9999)	0.48 (± 0.99)		
Dyspnoea, Week 95 (n=0, n=6)	9999 (± 9999)	0.87 (± 1.32)		
Dyspnoea, Week 96 (n=0, n=6)	9999 (± 9999)	1.13 (± 1.24)		
Dyspnoea, Week 97 (n=0, n=7)	9999 (± 9999)	1.26 (± 1.35)		
Dyspnoea, Week 98 (n=0, n=6)	9999 (± 9999)	0.80 (± 1.19)		
Dyspnoea, Week 99 (n=0, n=4)	9999 (± 9999)	0.70 (± 1.58)		
Dyspnoea, Week 100 (n=0, n=5)	9999 (± 9999)	0.88 (± 1.38)		
Dyspnoea, Week 101 (n=0, n=6)	9999 (± 9999)	1.13 (± 1.54)		
Dyspnoea, Week 102 (n=0, n=5)	9999 (± 9999)	0.96 (± 1.58)		
Dyspnoea, Week 103 (n=0, n=4)	9999 (± 9999)	0.55 (± 1.68)		
Dyspnoea, Week 104 (n=0, n=3)	9999 (± 9999)	1.07 (± 1.33)		
Dyspnoea, Week 105 (n=0, n=3)	9999 (± 9999)	1.07 (± 1.33)		

Dyspnoea, Week 106 (n=0, n=2)	9999 (± 9999)	0.40 (± 0.28)		
Dyspnoea, Week 107 (n=0, n=3)	9999 (± 9999)	1.13 (± 1.63)		
Dyspnoea, Week 108 (n=0, n=2)	9999 (± 9999)	1.50 (± 1.56)		
Dyspnoea, Week 109 (n=0, n=2)	9999 (± 9999)	1.30 (± 1.27)		
Dyspnoea, Week 110 (n=0, n=2)	9999 (± 9999)	1.50 (± 1.56)		
Dyspnoea, Week 111 (n=0, n=2)	9999 (± 9999)	1.60 (± 1.41)		
Dyspnoea, Week 112 (n=0, n=2)	9999 (± 9999)	1.50 (± 1.56)		
Dyspnoea, Week 113 (n=0, n=2)	9999 (± 9999)	1.50 (± 1.56)		
Dyspnoea, Week 114 (n=0, n=2)	9999 (± 9999)	1.60 (± 1.70)		
Dyspnoea, Week 115 (n=0, n=2)	9999 (± 9999)	1.40 (± 1.41)		
Dyspnoea, Week 116 (n=0, n=2)	9999 (± 9999)	1.30 (± 1.27)		
Dyspnoea, Week 117 (n=0, n=2)	9999 (± 9999)	1.50 (± 1.56)		
Dyspnoea, Week 118 (n=0, n=2)	9999 (± 9999)	1.30 (± 1.27)		
Dyspnoea, Week 119 (n=0, n=2)	9999 (± 9999)	1.50 (± 1.56)		
Dyspnoea, Week 120 (n=0, n=1)	9999 (± 9999)	2.20 (± 999999)		
Dyspnoea, Week 121 (n=0, n=1)	9999 (± 9999)	2.40 (± 999999)		
Dyspnoea, Week 122 (n=0, n=1)	9999 (± 9999)	2.20 (± 999999)		
Dyspnoea, Week 123 (n=0, n=1)	9999 (± 9999)	2.20 (± 999999)		
Dyspnoea, Week 124 (n=0, n=1)	9999 (± 9999)	2.20 (± 999999)		
Dyspnoea, Week 125 (n=0, n=1)	9999 (± 9999)	2.20 (± 999999)		
Dyspnoea, Week 126 (n=0, n=1)	9999 (± 9999)	2.20 (± 999999)		
Dyspnoea, Week 127 (n=0, n=1)	9999 (± 9999)	2.20 (± 999999)		
Dyspnoea, Week 128 (n=0, n=1)	9999 (± 9999)	2.20 (± 999999)		
Dyspnoea, Week 129 (n=0, n=1)	9999 (± 9999)	2.20 (± 999999)		
Dyspnoea, Week 130 (n=0, n=1)	9999 (± 9999)	2.20 (± 999999)		
Dyspnoea, Week 131 (n=0, n=1)	9999 (± 9999)	2.20 (± 999999)		

Statistical analyses

No statistical analyses for this end point

Secondary: TTD as Assessed Using EORTC QLQ Supplementary Lung Cancer Module (EORTC QLQ-LC13) in the TC3 or IC3-WT Populations

End point title	TTD as Assessed Using EORTC QLQ Supplementary Lung Cancer Module (EORTC QLQ-LC13) in the TC3 or IC3-WT Populations

End point description:

TTD in patient-reported lung cancer symptoms, defined as time from randomization to deterioration (10-point change) in any of the following symptom subscales (cough, dyspnea [multi-item scale], and chest pain), whichever occurs first, as measured by the EORTC QLQ-LC13. EORTC QLQ-LC13 module incorporates one multi-item scale to assess dyspnea and a series of single items assessing pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and hemoptysis. Note: 999999=not estimable.

End point type	Secondary

End point timeframe:

Baseline until data cut-off on 10 September 2018 (up to approximately 38 months)

End point values	Chemotherapy	Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	107		
Units: Months				
median (confidence interval 95%)				
Cough (n=98, n=107)	999999 (999999 to 999999)	999999 (21.5 to 999999)		
Dyspnea(n=98, n=107)	11.8 (6.8 to 19.5)	11.1 (7.0 to 999999)		
Chest pain(n=98, n=107)	999999 (999999 to 999999)	999999 (999999 to 999999)		

Statistical analyses

Statistical analysis title	TTD Using EORTC QLQ-LC13 Statistical Analysis

Statistical analysis description:

Cough for TC3 or IC3-WT Populations

Comparison groups	Chemotherapy v Atezolizumab
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority[20]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.984
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.477
upper limit	2.03

Notes:

[20] - Stratified analysis

Statistical analysis title	TTD Using EORTC QLQ-LC13 Statistical Analysis

Statistical analysis description:

Chest pain for TC3 or IC3-WT Populations

Comparison groups	Chemotherapy v Atezolizumab

Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority[21]
Parameter estimate	Hazard ratio (HR)
Point estimate	1.024
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.472
upper limit	2.222

Notes:

[21] - Stratified analysis

Statistical analysis title	TTD Using EORTC QLQ-LC13 Statistical Analysis

Statistical analysis description:

Dyspnea for TC3 or IC3-WT Populations

Comparison groups	Chemotherapy v Atezolizumab
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority[22]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.955
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.569
upper limit	1.604

Notes:

[22] - Stratified analysis

Secondary: OS in Participants with PD-L1 Expression

End point title	OS in Participants with PD-L1 Expression

End point description:

OS is defined as the time from randomization to death from any cause. Note: 999999=not estimable.

End point type	Secondary

End point timeframe:

From randomization to death from any cause until data cut-off on 10 September 2018 (up to approximately 38 months)

End point values	Chemotherapy	Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210	212		
Units: Months				
median (confidence interval 95%)				
SP263 >=50%-WT Population (n=143, n=150)	16.1 (9.8 to 17.4)	19.5 (13.8 to 999999)		
SP263 >=25%-WT Population (n=168, n=168)	12.6 (9.1 to 17.0)	18.2 (13.3 to 999999)		

SP263 =1%-WT Population(n=210, n=212)	14.0 (9.8 to 16.5)	17.8 (12.8 to 23.1)		

Statistical analyses

Statistical analysis title	OS in Participants With PD-L1 Statistical Analysis
Statistical analysis description: SP263 >=50%-WT Population	
Comparison groups	Chemotherapy v Atezolizumab
Number of subjects included in analysis	422
Analysis specification	Pre-specified
Analysis type	superiority[23]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.707
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1

Notes:
[23] - Unstratified analysis

Statistical analysis title	OS in Participants With PD-L1 Statistical Analysis
Statistical analysis description: SP263 >=1%-WT Population	
Comparison groups	Chemotherapy v Atezolizumab
Number of subjects included in analysis	422
Analysis specification	Pre-specified
Analysis type	superiority[24]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.768
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.579
upper limit	1.018

Notes:
[24] - Unstratified analysis

Statistical analysis title	OS in Participants With PD-L1 Statistical Analysis
Statistical analysis description: SP263 >=25%-WT Population	
Comparison groups	Chemotherapy v Atezolizumab

Number of subjects included in analysis	422
Analysis specification	Pre-specified
Analysis type	superiority[25]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.693
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.502
upper limit	0.956

Notes:

[25] - Unstratified analysis

Secondary: Investigator-Assessed PFS in Participants with PD-L1 Expression According to RECIST v1.1

End point title	Investigator-Assessed PFS in Participants with PD-L1 Expression According to RECIST v1.1

End point description:

Investigator-assessed PFS according to RECIST v1.1 in the PD-L1 (defined with SP263 IHC assay)

End point type	Secondary

End point timeframe:

From randomization to the first occurrence of disease progression or death from any cause, whichever occurs first until data cut-off on 10 September 2018 (up to approximately 38 months)

End point values	Chemotherapy	Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210	212		
Units: Months				
median (confidence interval 95%)				
SP263 >=50%-WT Population (n=143, n=150)	4.9 (4.0 to 5.6)	7.0 (5.6 to 8.7)		
SP263 >=25%-WT Population(n=168, n=168)	4.9 (4.2 to 5.6)	6.9 (5.6 to 8.4)		
SP263 >=1%-WT Population(n=210, n=212)	5.4 (4.4 to 5.7)	6.8 (5.5 to 8.0)		

Statistical analyses

Statistical analysis title	Investigator-Assessed PFS Statistical Analysis

Statistical analysis description:

SP263 >=50%-WT Population

Comparison groups	Chemotherapy v Atezolizumab

Number of subjects included in analysis	422
Analysis specification	Pre-specified
Analysis type	superiority[26]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.674
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.511
upper limit	0.89

Notes:
[26] - Unstratified analysis

Statistical analysis title	Investigator-Assessed PFS Statistical Analysis
Statistical analysis description:	
SP263 >=1%-WT Population	
Comparison groups	Chemotherapy v Atezolizumab
Number of subjects included in analysis	422
Analysis specification	Pre-specified
Analysis type	superiority[27]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.725
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.577
upper limit	0.91

Notes:
[27] - Unstratified analysis

Statistical analysis title	Investigator-Assessed PFS Statistical Analysis
Statistical analysis description:	
SP263 >=25%-WT Population	
Comparison groups	Chemotherapy v Atezolizumab
Number of subjects included in analysis	422
Analysis specification	Pre-specified
Analysis type	superiority[28]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.698
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.539
upper limit	0.904

Notes:
[28] - Unstratified analysis

Secondary: OS in Participants with Blood Tumor Mutational Burden (bTMB)

End point title	OS in Participants with Blood Tumor Mutational Burden (bTMB)

End point description:

OS is defined as the time from randomization to death from any cause. Note: 999999=not estimable.

End point type	Secondary

End point timeframe:

From randomization to death from any cause until data cut-off on 10 September 2018 (up to approximately 38 months)

End point values	Chemotherapy	Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	92		
Units: Months				
median (confidence interval 95%)				
bTMB >=10-WT Population (n=83, n=92)	10.3 (7.1 to 16.9)	11.2 (7.9 to 999999)		
bTMB >=16-WT Population(n=45, n=42)	8.5 (5.8 to 999999)	13.9 (10.8 to 999999)		
bTMB >=20-WT Population(n=29, n=27)	10.5 (5.8 to 999999)	17.2 (10.8 to 999999)		

Statistical analyses

Statistical analysis title	OS in Participants with bTMB

Statistical analysis description:

bTMB >=10-WT Population

Comparison groups	Chemotherapy v Atezolizumab
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	superiority[29]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.867
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.578
upper limit	1.301

Notes:

[29] - Unstratified analysis

Statistical analysis title	OS in Participants with bTMB

Statistical analysis description:

bTMB >=20-WT Population

Comparison groups	Chemotherapy v Atezolizumab

Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	superiority[30]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.362
upper limit	1.638

Notes:

[30] - Unstratified analysis

Statistical analysis title	OS in Participants with bTMB

Statistical analysis description:

bTMB >=16-WT Population

Comparison groups	Chemotherapy v Atezolizumab
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	superiority[31]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.748
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.414
upper limit	1.351

Notes:

[31] - Unstratified analysis

Secondary: Investigator-Assessed PFS in Participants with bTMB According to RECIST v1.1

End point title	Investigator-Assessed PFS in Participants with bTMB According to RECIST v1.1

End point description:

PFS according to RECIST v1.1 in the bTMB subpopulations.

End point type	Secondary

End point timeframe:

From randomization to the first occurrence of disease progression or death from any cause, whichever occurs first until data cut-off on 10 September 2018 (up to approximately 38 months)

End point values	Chemotherapy	Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	92		
Units: Months				
median (confidence interval 95%)				
bTMB >=10-WT Population (n=83, n=92)	4.3 (3.1 to 5.4)	5.5 (2.8 to 6.8)		

bTMB >=16-WT Population(n=45, n=42)	4.4 (2.8 to 5.7)	6.8 (4.3 to 11.6)		
bTMB >=20-WT Population(n=29, n=27)	5.2 (3.2 to 6.4)	6.8 (4.3 to 17.2)		

Statistical analyses

Statistical analysis title	Investigator-Assessed PFS Statistical Analysis
Statistical analysis description: bTMB >=10-WT Population	
Comparison groups	Chemotherapy v Atezolizumab
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	superiority[32]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.743
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.525
upper limit	1.052

Notes:
[32] - Unstratified analysis

Statistical analysis title	Investigator-Assessed PFS Statistical Analysis
Statistical analysis description: bTMB >=20-WT Population	
Comparison groups	Chemotherapy v Atezolizumab
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	superiority[33]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.295
upper limit	1.062

Notes:
[33] - Unstratified analysis

Statistical analysis title	Investigator-Assessed PFS Statistical Analysis
Statistical analysis description: bTMB >=16-WT Population	
Comparison groups	Chemotherapy v Atezolizumab

Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	superiority[34]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.553
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.331
upper limit	0.924

Notes:

[34] - Unstratified analysis

Secondary: Minimum Observed Serum Concentration (Cmin) of Atezolizumab

End point title	Minimum Observed Serum Concentration (Cmin) of Atezolizumab[35]

End point description:

Note: 999999=not estimable.

End point type	Secondary

End point timeframe:

Prior to infusion (0 hour) on Day 1 of Cycles 2, 3, 4, 8, 16, and every eighth cycle thereafter, and at treatment discontinuation until data cut-off on 10 September 2018 (up to approximately 38 months) (cycle duration = 21 days)

Notes:

[35] - 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: No statistical analysis for this end point.

End point values	Atezolizumab			
Subject group type	Reporting group			
Number of subjects analysed	256			
Units: micrograms per milliliter (µg/ mL)				
arithmetic mean (standard deviation)				
Cycle 2 Day 1 (n=256)	76.7 (± 57.6)			
Cycle 3 Day 1 (n=215)	121 (± 57.7)			
Cycle 4 Day 1 (n=207)	154 (± 90.1)			
Cycle 8 Day 1 (n=145)	201 (± 98.6)			
Cycle 16 Day 1 (n=67)	213 (± 102)			
Cycle 24 Day 1 (n=31)	245 (± 128)			
Cycle 32 Day 1 (n=10)	276 (± 110)			
Cycle 40 Day 1 (n=5)	252 (± 160)			
Cycle 48 Day 1 (n=1)	555 (± 999999)			
Treatment Discontinuation Visit (n=100)	121 (± 88.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Serum Concentration (Cmax) of Atezolizumab

End point title	Maximum Observed Serum Concentration (Cmax) of Atezolizumab[36]

End point description:

End point type	Secondary

End point timeframe:

0 hour (predose) and 30 minutes after atezolizumab infusion on Day 1 (infusion duration = up to 1 hour)

Notes:

[36] - 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: No statistical analysis for this end point.

End point values	Atezolizumab			
Subject group type	Reporting group			
Number of subjects analysed	270			
Units: micrograms per milliliter (µg/ mL)				
arithmetic mean (standard deviation)	411 (± 163)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With at Least One Adverse Event

End point title	Percentage of Participants With at Least One Adverse Event

End point description:

Percentage of participants with at least one adverse event in the Safety Population. Safety analyses included treated participants, defined as randomized participants who received any amount of study treatment.

End point type	Secondary

End point timeframe:

Baseline up to until data cut-off on 8 March 2022 (up to approximately 79.5 months)

End point values	Chemotherapy Safety Population	Atezolizumab Safety Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	263	286		
Units: Percentage of participants				
number (not applicable)	95.1	92.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Anti-therapeutic Antibodies (ATAs)

End point title	Percentage of Participants With Anti-therapeutic Antibodies (ATAs)[37]

End point description:

End point type	Secondary

End point timeframe:

Baseline until data cut-off on 10 September 2018 (up to approximately 38 months)

Notes:

[37] - 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: No statistical analysis for this end point.

End point values	Atezolizumab			
Subject group type	Reporting group			
Number of subjects analysed	282			
Units: Percentage of participants				
number (not applicable)				
Baseline evaluable participants (n=282)	1.4			
Post-baseline evaluable participants (n=267)	24.3			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first study drug until the data cut-off on 8 March 2022 (up to approximately 79.5 months).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Atezolizumab

Reporting group description:

Participants with squamous or non-squamous NSCLC will receive atezolizumab on Day 1 of each 21-day cycle until loss of clinical benefit (as assessed by the investigator), unacceptable toxicity, or death (maximum up to approximately 58 months).

Reporting group title	Chemotherapy

Reporting group description:

Participants with non-squamous NSCLC will receive chemotherapy with pemetrexed in combination with either cisplatin or carboplatin (per investigator discretion) on Day 1 of each 21-day cycle for 4 or 6 cycles as per local standard of care, followed by maintenance therapy with pemetrexed alone as per local standard of care until disease progression (per RECIST v1.1), unacceptable toxicity, or death (maximum up to approximately 58 months).

Participants with squamous NSCLC will receive chemotherapy with gemcitabine on Days 1 and 8 of each 21-day cycle in combination with either cisplatin or carboplatin on Day 1 of each 21-day cycle for 4 or 6 cycles as per local standard of care, followed by best supportive care as per local standard of care until disease progression, unacceptable toxicity, or death (maximum up to approximately 58 months).

Serious adverse events	Atezolizumab	Chemotherapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	97 / 286 (33.92%)	77 / 263 (29.28%)	
number of deaths (all causes)	213	212	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Transitional cell carcinoma			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma gastric			
subjects affected / exposed	0 / 286 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary neoplasm			

subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal cancer			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic neoplasm			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Langerhans' cell histiocytosis			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Thrombophlebitis			
subjects affected / exposed	0 / 286 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava syndrome			
subjects affected / exposed	1 / 286 (0.35%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extremity necrosis			
subjects affected / exposed	0 / 286 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			

subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm rupture			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Varicose vein			
subjects affected / exposed	0 / 286 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vein disorder			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cataract operation			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Swelling			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	4 / 286 (1.40%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	3 / 286 (1.05%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fatigue			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (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	2 / 286 (0.70%)	3 / 263 (1.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 3	
Asthenia			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Immune system disorder			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemophagocytic lymphohistiocytosis			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	0 / 286 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic reaction			
subjects affected / exposed	2 / 286 (0.70%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			

subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 286 (0.00%)	4 / 263 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 286 (0.70%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	8 / 286 (2.80%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 14	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Aspiration			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	0 / 286 (0.00%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonitis			
subjects affected / exposed	6 / 286 (2.10%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	10 / 10	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 286 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			

subjects affected / exposed	0 / 286 (0.00%)	1 / 263 (0.38%)	
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	6 / 286 (2.10%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 6	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchial obstruction			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 286 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Thrombosis in device			
subjects affected / exposed	0 / 286 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device occlusion			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	0 / 286 (0.00%)	1 / 263 (0.38%)	
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			
Femur fracture			
subjects affected / exposed	0 / 286 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	2 / 286 (0.70%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Radiation pneumonitis			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	2 / 286 (0.70%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 286 (0.35%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune myocarditis			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 286 (0.35%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Cardiac failure			
subjects affected / exposed	0 / 286 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial ischaemia			
subjects affected / exposed	0 / 286 (0.00%)	1 / 263 (0.38%)	
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 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Supraventricular tachycardia			

subjects affected / exposed	0 / 286 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	1 / 286 (0.35%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid arteriosclerosis			
subjects affected / exposed	0 / 286 (0.00%)	1 / 263 (0.38%)	
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	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Seizure			
subjects affected / exposed	1 / 286 (0.35%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological decompensation			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			

subjects affected / exposed	0 / 286 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 286 (0.00%)	5 / 263 (1.90%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 286 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 286 (0.00%)	5 / 263 (1.90%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 286 (0.00%)	3 / 263 (1.14%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Thrombocytopenia			
subjects affected / exposed	1 / 286 (0.35%)	9 / 263 (3.42%)	
occurrences causally related to treatment / all	1 / 1	10 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytosis			
subjects affected / exposed	0 / 286 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 286 (0.35%)	10 / 263 (3.80%)	
occurrences causally related to treatment / all	0 / 1	14 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Cataract			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 286 (0.35%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal motility disorder			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 286 (0.35%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (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 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 286 (0.00%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			

subjects affected / exposed	1 / 286 (0.35%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune colitis			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical ileus			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nausea			
subjects affected / exposed	0 / 286 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 286 (0.35%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 286 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis			

subjects affected / exposed	2 / 286 (0.70%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	0 / 286 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune dermatitis			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute febrile neutrophilic dermatosis			
subjects affected / exposed	0 / 286 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic skin eruption			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (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			
Renal impairment			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			

subjects affected / exposed	0 / 286 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ketonuria			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Glucocorticoid deficiency			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Pathological fracture			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fistula			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess neck			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural infection			
subjects affected / exposed	0 / 286 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia			
subjects affected / exposed	15 / 286 (5.24%)	14 / 263 (5.32%)	
occurrences causally related to treatment / all	0 / 25	3 / 14	
deaths causally related to treatment / all	0 / 1	0 / 1	
Mycotic endophthalmitis			
subjects affected / exposed	0 / 286 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle abscess			
subjects affected / exposed	0 / 286 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	3 / 286 (1.05%)	3 / 263 (1.14%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 286 (0.70%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			

subjects affected / exposed	0 / 286 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis bacterial			
subjects affected / exposed	1 / 286 (0.35%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 286 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periodontitis			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 286 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	0 / 286 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			

subjects affected / exposed	3 / 286 (1.05%)	4 / 263 (1.52%)	
occurrences causally related to treatment / all	0 / 3	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis			
subjects affected / exposed	2 / 286 (0.70%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	0 / 286 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			
subjects affected / exposed	0 / 286 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Upper respiratory tract infection			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	2 / 286 (0.70%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial colitis			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	2 / 286 (0.70%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post-acute COVID-19 syndrome			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Tumour lysis syndrome			
subjects affected / exposed	0 / 286 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	3 / 286 (1.05%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	3 / 286 (1.05%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	0 / 286 (0.00%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	1 / 286 (0.35%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Atezolizumab	Chemotherapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	238 / 286 (83.22%)	230 / 263 (87.45%)	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	29 / 286 (10.14%)	11 / 263 (4.18%)	
occurrences (all)	35	12	
Blood creatinine increased			
subjects affected / exposed	9 / 286 (3.15%)	27 / 263 (10.27%)	
occurrences (all)	12	33	
Alanine aminotransferase increased			
subjects affected / exposed	30 / 286 (10.49%)	16 / 263 (6.08%)	
occurrences (all)	34	17	
Neutrophil count decreased			
subjects affected / exposed	0 / 286 (0.00%)	19 / 263 (7.22%)	
occurrences (all)	0	27	
White blood cell count decreased			
subjects affected / exposed	3 / 286 (1.05%)	14 / 263 (5.32%)	
occurrences (all)	17	24	
Weight decreased			
subjects affected / exposed	25 / 286 (8.74%)	15 / 263 (5.70%)	
occurrences (all)	27	15	
Platelet count decreased			
subjects affected / exposed	1 / 286 (0.35%)	21 / 263 (7.98%)	
occurrences (all)	1	30	
Nervous system disorders			
Headache			
subjects affected / exposed	31 / 286 (10.84%)	18 / 263 (6.84%)	
occurrences (all)	32	20	
Dizziness			

subjects affected / exposed	9 / 286 (3.15%)	14 / 263 (5.32%)	
occurrences (all)	9	18	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	4 / 286 (1.40%)	21 / 263 (7.98%)	
occurrences (all)	6	31	
Anaemia			
subjects affected / exposed	50 / 286 (17.48%)	120 / 263 (45.63%)	
occurrences (all)	73	153	
Thrombocytopenia			
subjects affected / exposed	8 / 286 (2.80%)	40 / 263 (15.21%)	
occurrences (all)	8	62	
Neutropenia			
subjects affected / exposed	5 / 286 (1.75%)	71 / 263 (27.00%)	
occurrences (all)	7	128	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	40 / 286 (13.99%)	25 / 263 (9.51%)	
occurrences (all)	58	30	
Fatigue			
subjects affected / exposed	44 / 286 (15.38%)	47 / 263 (17.87%)	
occurrences (all)	47	57	
Chest pain			
subjects affected / exposed	21 / 286 (7.34%)	10 / 263 (3.80%)	
occurrences (all)	28	10	
Asthenia			
subjects affected / exposed	41 / 286 (14.34%)	47 / 263 (17.87%)	
occurrences (all)	58	66	
Oedema peripheral			
subjects affected / exposed	13 / 286 (4.55%)	16 / 263 (6.08%)	
occurrences (all)	14	18	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	42 / 286 (14.69%)	88 / 263 (33.46%)	
occurrences (all)	49	148	
Diarrhoea			

subjects affected / exposed	39 / 286 (13.64%)	30 / 263 (11.41%)	
occurrences (all)	55	39	
Constipation			
subjects affected / exposed	42 / 286 (14.69%)	58 / 263 (22.05%)	
occurrences (all)	48	75	
Vomiting			
subjects affected / exposed	21 / 286 (7.34%)	34 / 263 (12.93%)	
occurrences (all)	27	45	
Stomatitis			
subjects affected / exposed	12 / 286 (4.20%)	14 / 263 (5.32%)	
occurrences (all)	14	16	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	36 / 286 (12.59%)	25 / 263 (9.51%)	
occurrences (all)	48	27	
Dyspnoea			
subjects affected / exposed	41 / 286 (14.34%)	26 / 263 (9.89%)	
occurrences (all)	48	32	
Haemoptysis			
subjects affected / exposed	23 / 286 (8.04%)	9 / 263 (3.42%)	
occurrences (all)	25	12	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	23 / 286 (8.04%)	8 / 263 (3.04%)	
occurrences (all)	26	8	
Pruritus			
subjects affected / exposed	25 / 286 (8.74%)	4 / 263 (1.52%)	
occurrences (all)	33	4	
Alopecia			
subjects affected / exposed	3 / 286 (1.05%)	16 / 263 (6.08%)	
occurrences (all)	3	16	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	22 / 286 (7.69%)	15 / 263 (5.70%)	
occurrences (all)	25	16	
Endocrine disorders			

Hypothyroidism			
subjects affected / exposed	27 / 286 (9.44%)	3 / 263 (1.14%)	
occurrences (all)	28	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	31 / 286 (10.84%)	8 / 263 (3.04%)	
occurrences (all)	46	8	
Back pain			
subjects affected / exposed	26 / 286 (9.09%)	14 / 263 (5.32%)	
occurrences (all)	28	15	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	22 / 286 (7.69%)	7 / 263 (2.66%)	
occurrences (all)	37	8	
Pneumonia			
subjects affected / exposed	15 / 286 (5.24%)	8 / 263 (3.04%)	
occurrences (all)	17	8	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	19 / 286 (6.64%)	12 / 263 (4.56%)	
occurrences (all)	29	19	
Decreased appetite			
subjects affected / exposed	50 / 286 (17.48%)	50 / 263 (19.01%)	
occurrences (all)	65	61	
Hyperglycaemia			
subjects affected / exposed	12 / 286 (4.20%)	15 / 263 (5.70%)	
occurrences (all)	18	17	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 October 2015	Protocol was amended to include modification of inclusion criteria to allow for patients with treated, asymptomatic cerebellar metastases to be enrolled provided specific criteria were met. The exclusion criteria for history of autoimmune disease was broadened to allow for patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only to be permitted provided that they met the specific conditions. The exclusion criterion specifying that patients with a history of allergic reaction to IV contrast that requires steroid pretreatment should have baseline and subsequent tumor assessments performed via MRI was removed.
16 December 2015	Protocol was amended to include clarification that a wash-out period of at least 4 weeks or five half-lives, whichever was longer, of any systemic immunostimulatory agent was required prior to randomization.
29 June 2016	Protocol was amended to expand the patient population to include patients with squamous NSCLC, who was randomized to receive either atezolizumab or chemotherapy consisting of a platinum agent (carboplatin or cisplatin per investigator discretion) combined with gemcitabine (in contrast to patients with non-squamous NSCLC, who received either atezolizumab or chemotherapy consisting of a platinum agent combined with pemetrexed). Cuff-off revised for PD-L1 expression in TCs and ICs to allow for inclusion of patients with TC1/2/3 or IC1/2/3 instead of TC3 of IC3. Co-primary endpoint of OS in addition to PFS endpoint was added. Stratification factors were modified. The timing of the primary PFS analysis and the definition of end of study were updated.
14 March 2017	Protocol was amended to exclude patients with a known sensitizing EGFR mutation or ALK translocation from the study. Investigator-assessed PFS was changed to a secondary endpoint and maintained OS as the primary endpoint. The secondary objective and outcome measure regarding independent review facility (IRF)-assessed PFS according to RECIST v1.1 have been removed. Modifications were made to the statistical testing procedure for the primary efficacy endpoint (OS). The sample size was changed from 570 to 555 patients.
16 April 2018	Protocol was amended to include modification of the number of OS events required in the TC2/3 or tumor-infiltrating IC2/3WT subgroup due to lower PD-L1 prevalence of TC2/3 or IC2/3-WT than the previous protocol assumption. Secondary endpoints to evaluate OS and PFS in patients with PD-L1 expression defined by the SP263 IHC assay and in patients with bTMB, including bTMB >=10, and bTMB >=16 were added.
29 August 2018	Protocol was amended to include modification to the timing of the interim efficacy analysis.

14 March 2019	Protocol was amended to include addition of the TC3 or IC3 population excluding patients with a sensitizing EGFR mutation or ALK translocation (i.e.; TC3 or IC3-WT) as the first testing hierarchy. The timing of the interim efficacy analysis was changed to be conducted when the prespecified criteria was met for the TC3 or IC3-WT population. The secondary endpoints for OS and investigator-assessed PFS in patients defined by the SP263 IHC assay were being updated to include the validated PD-L1 tumor expression cutoff of >=25% (in addition to >=1% and >=50%) in order to evaluate this additional PD-L1 expression level with respect to efficacy. The secondary endpoints for OS and investigator-assessed PFS in patients defined by the bTMB assay were being updated to include the 20 mutations cutoff (in addition to 10 and 16 mutations), in order to evaluate this additional TMB level with respect to efficacy. It was clarified that the primary safety analyses included all treated patients, defined as randomized patients who received any amount of study treatment, regardless of EGFR/ALK and PD-L1 status.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported