Clinical trial results:
A Phase III, Open-Label, Multicenter, Randomized Study Evaluating the Efficacy and Safety of Atezolizumab (MPDL3280A, Anti-PD-L1 Antibody) in Combination With Carboplatin+Paclitaxel or Atezolizumab in Combination With Carboplatin+Nab-Paclitaxel Versus Carboplatin+Nab-Paclitaxel in Chemotherapy-Naive Patients With Stage IV Squamous Non-Small Cell Lung Cancer

Summary

EudraCT number	2014-003208-59
Trial protocol	IT LV DE AT BE ES NL LT BG PT FR SK
Global end of trial date	

Results information

Result version number	v1
This version publication date	13 October 2019
First version publication date	13 October 2019

Trial information

Trial identification

Sponsor protocol code	GO29437

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02367794
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland,
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	Interim
Date of interim/final analysis	03 October 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 October 2018
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this randomized, Phase III, multicenter, open-label study was to evaluate the safety and efficacy of atezolizumab in combination with carboplatin + paclitaxel or with carboplatin + nab-paclitaxel compared with treatment with carboplatin + nab-paclitaxel in approximately 1025 chemotherapy-naive patients with Stage IV squamous non-small cell lung cancer (NSCLC).

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	11 June 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 12
Country: Number of subjects enrolled	Australia: 33
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Belgium: 16
Country: Number of subjects enrolled	Bulgaria: 9
Country: Number of subjects enrolled	Brazil: 27
Country: Number of subjects enrolled	Canada: 16
Country: Number of subjects enrolled	Chile: 20
Country: Number of subjects enrolled	Germany: 72
Country: Number of subjects enrolled	Spain: 142
Country: Number of subjects enrolled	France: 35
Country: Number of subjects enrolled	Israel: 21
Country: Number of subjects enrolled	Italy: 37
Country: Number of subjects enrolled	Japan: 83
Country: Number of subjects enrolled	Lithuania: 1
Country: Number of subjects enrolled	Latvia: 12
Country: Number of subjects enrolled	Mexico: 4
Country: Number of subjects enrolled	Netherlands: 16
Country: Number of subjects enrolled	Peru: 6
Country: Number of subjects enrolled	Portugal: 12
Country: Number of subjects enrolled	Russian Federation: 35
Country: Number of subjects enrolled	Singapore: 12

Country: Number of subjects enrolled	Slovakia: 6
Country: Number of subjects enrolled	Taiwan: 12
Country: Number of subjects enrolled	Ukraine: 178
Country: Number of subjects enrolled	United States: 201
Worldwide total number of subjects	1021
EEA total number of subjects	361

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)	476
From 65 to 84 years	543
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects in this study included chemotherapy-naive patients with Stage IV squamous non-small cell lung cancer (NSCLC).

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	Arm C: Nab-Paclitaxel + Carboplatin

Arm description:

The induction phase of the study consisted of four or six cycles; carboplatin was administered on Day 1 of each 21-day cycle, nab-paclitaxel was administered on Days 1, 8, and 15 of each 21-day cycle. The Day 1 order of drug administration was as follows: nab-paclitaxel, then carboplatin. Subjects who experienced disease progression at any time during the induction phase discontinued all study treatment. In the maintenance phase, subjects received best supportive care.

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

Dosage and administration details:

Nab-paclitaxel 100 milligrams per meter squared (mg/m^2) IV on Day 1, 8, and 15 of each 21-day cycle for 4 or 6 cycles.

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

Dosage and administration details:

Carboplatin area under the concentration curve (AUC) 6 milligrams per milliliter per minute (mg/mL/min) on Day 1 of each 21-day cycle for 4 or 6 cycles.

Arm title	Arm B: Atezolizumab + Nab-Paclitaxel + Carboplatin

Arm description:

The induction phase of the study consisted of four or six cycles; atezolizumab and carboplatin were administered on Day 1 of each 21-day cycle. Nab-Paclitaxel was administered on Days 1, 8, and 15 of each 21-day cycle. The Day 1 order of drug administration was as follows: atezolizumab, then nab-paclitaxel, then carboplatin. Subjects who experienced no further clinical benefit at any time during the induction phase discontinued all study treatments. In the absence of the above criteria, after the 4- or 6-cycle induction phase, subjects began maintenance therapy with atezolizumab. Atezolizumab was continued as long as there was clinical benefit to the subject.

Arm type	Experimental

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

Dosage and administration details:

Atezolizumab 1200 milligrams (mg) intravenous infusion (IV) on day 1 of each 21-day cycle.

Investigational medicinal product name	Nab-Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Nab-paclitaxel 100 milligrams per meter squared (mg/m^2) IV on Day 1, 8, and 15 of each 21-day cycle for 4 or 6 cycles

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

Dosage and administration details:

Carboplatin area under the concentration curve (AUC) 6 milligrams per milliliter per minute (mg/mL/min) on Day 1 of each 21-day cycle for 4 or 6 cycles.

Arm title	Arm A: Atezolizumab + Paclitaxel + Carboplatin

Arm description:

The induction phase of the study consisted of four or six cycles; atezolizumab, paclitaxel, and carboplatin were administered on Day 1 of each 21-day cycle. The Day 1 order of drug administration was as follows: atezolizumab, then paclitaxel, then carboplatin. Subjectss who experienced no further clinical benefit at any time during the induction phase discontinued all study treatments. In the absence of the above criteria, after the 4- or 6-cycle induction phase, subjects began maintenance therapy with atezolizumab. Atezolizumab was continued as long as there was clinical benefit to the subject.

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

Dosage and administration details:

Paclitaxel 200 mg/m^2 IV on Day 1 of each 21-day cycle for 4 or 6 cycles. Participants of Asian race/ethnicity will be administered paclitaxel 175 mg/m2 IV.

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use , Intravenous use

Dosage and administration details:

Carboplatin area under the concentration curve (AUC) 6 milligrams per milliliter per minute (mg/mL/min) on Day 1 of each 21-day cycle for 4 or 6 cycles.

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

Dosage and administration details:
Atezolizumab 1200 milligrams (mg) intravenous infusion (IV) on day 1 of each 21-day cycle.

Number of subjects in period 1	Arm C: Nab-Paclitaxel + Carboplatin	Arm B: Atezolizumab + Nab-Paclitaxel + Carboplatin	Arm A: Atezolizumab + Paclitaxel + Carboplatin
Started	340	343	338
Completed	82	103	89
Not completed	258	240	249
Randomized in error	-	-	1
Consent withdrawn by subject	25	12	14
Physician decision	-	3	1
Death	230	223	229
Patient unable to receive carboplatin	-	-	1
Lost to follow-up	1	2	1
Brain metastasis	1	-	-
Protocol deviation	1	-	1
Hypercalcemia prior to C1D1	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Arm C: Nab-Paclitaxel + Carboplatin

Reporting group description:

The induction phase of the study consisted of four or six cycles; carboplatin was administered on Day 1 of each 21-day cycle, nab-paclitaxel was administered on Days 1, 8, and 15 of each 21-day cycle. The Day 1 order of drug administration was as follows: nab-paclitaxel, then carboplatin. Subjects who experienced disease progression at any time during the induction phase discontinued all study treatment. In the maintenance phase, subjects received best supportive care.

Reporting group title	Arm B: Atezolizumab + Nab-Paclitaxel + Carboplatin

Reporting group description:

The induction phase of the study consisted of four or six cycles; atezolizumab and carboplatin were administered on Day 1 of each 21-day cycle. Nab-Paclitaxel was administered on Days 1, 8, and 15 of each 21-day cycle. The Day 1 order of drug administration was as follows: atezolizumab, then nab-paclitaxel, then carboplatin. Subjects who experienced no further clinical benefit at any time during the induction phase discontinued all study treatments. In the absence of the above criteria, after the 4- or 6-cycle induction phase, subjects began maintenance therapy with atezolizumab. Atezolizumab was continued as long as there was clinical benefit to the subject.

Reporting group title	Arm A: Atezolizumab + Paclitaxel + Carboplatin

Reporting group description:

The induction phase of the study consisted of four or six cycles; atezolizumab, paclitaxel, and carboplatin were administered on Day 1 of each 21-day cycle. The Day 1 order of drug administration was as follows: atezolizumab, then paclitaxel, then carboplatin. Subjectss who experienced no further clinical benefit at any time during the induction phase discontinued all study treatments. In the absence of the above criteria, after the 4- or 6-cycle induction phase, subjects began maintenance therapy with atezolizumab. Atezolizumab was continued as long as there was clinical benefit to the subject.

Reporting group values	Arm C: Nab-Paclitaxel + Carboplatin	Arm B: Atezolizumab + Nab-Paclitaxel + Carboplatin	Arm A: Atezolizumab + Paclitaxel + Carboplatin
Number of subjects	340	343	338
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)	156	170	150
From 65-84 years	183	173	187
85 years and over	1	0	1
Age Continuous Units: Years			
arithmetic mean	64.9	64.0	65.0
standard deviation	± 8.1	± 9.2	± 8.3
Sex: Female, Male Units: Subjects			
Female	63	63	60
Male	277	280	278

Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	24	27	28
Not Hispanic or Latino	299	306	297
Unknown or Not Reported	17	10	13
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	1	3
Asian	37	41	34
Native Hawaiian or Other Pacific Islander	0	0	1
Black or African American	7	4	3
White	290	289	290
More than one race	1	6	1
Unknown or Not Reported	4	2	6

Reporting group values	Total		
Number of subjects	1021		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	476		
From 65-84 years	543		
85 years and over	2		
Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Subjects			
Female	186		
Male	835		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	79		
Not Hispanic or Latino	902		
Unknown or Not Reported	40		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	5		
Asian	112		
Native Hawaiian or Other Pacific Islander	1		
Black or African American	14		
White	869		
More than one race	8		

Unknown or Not Reported	12		

End points

End points reporting groups

Reporting group title	Arm C: Nab-Paclitaxel + Carboplatin

Reporting group description:

The induction phase of the study consisted of four or six cycles; carboplatin was administered on Day 1 of each 21-day cycle, nab-paclitaxel was administered on Days 1, 8, and 15 of each 21-day cycle. The Day 1 order of drug administration was as follows: nab-paclitaxel, then carboplatin. Subjects who experienced disease progression at any time during the induction phase discontinued all study treatment. In the maintenance phase, subjects received best supportive care.

Reporting group title	Arm B: Atezolizumab + Nab-Paclitaxel + Carboplatin

Reporting group description:

The induction phase of the study consisted of four or six cycles; atezolizumab and carboplatin were administered on Day 1 of each 21-day cycle. Nab-Paclitaxel was administered on Days 1, 8, and 15 of each 21-day cycle. The Day 1 order of drug administration was as follows: atezolizumab, then nab-paclitaxel, then carboplatin. Subjects who experienced no further clinical benefit at any time during the induction phase discontinued all study treatments. In the absence of the above criteria, after the 4- or 6-cycle induction phase, subjects began maintenance therapy with atezolizumab. Atezolizumab was continued as long as there was clinical benefit to the subject.

Reporting group title	Arm A: Atezolizumab + Paclitaxel + Carboplatin

Reporting group description:

The induction phase of the study consisted of four or six cycles; atezolizumab, paclitaxel, and carboplatin were administered on Day 1 of each 21-day cycle. The Day 1 order of drug administration was as follows: atezolizumab, then paclitaxel, then carboplatin. Subjectss who experienced no further clinical benefit at any time during the induction phase discontinued all study treatments. In the absence of the above criteria, after the 4- or 6-cycle induction phase, subjects began maintenance therapy with atezolizumab. Atezolizumab was continued as long as there was clinical benefit to the subject.

Primary: Progression Free Survival (PFS) as Determined by the Investigator Using Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) in the Intent-to-Treat (ITT) Population

End point title	Progression Free Survival (PFS) as Determined by the Investigator Using Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) in the Intent-to-Treat (ITT) Population

End point description:

PFS is defined as the time between the date of randomization and the date of first documented disease progression or death, whichever occurs first, in the ITT population.

End point type	Primary

End point timeframe:

Up to approximately 30 months after first participant enrolled

End point values	Arm C: Nab-Paclitaxel + Carboplatin	Arm B: Atezolizumab + Nab-Paclitaxel + Carboplatin	Arm A: Atezolizumab + Paclitaxel + Carboplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	340	343	338	
Units: Months				
median (confidence interval 95%)	5.6 (5.5 to 5.7)	6.5 (5.7 to 7.1)	5.6 (5.5 to 6.9)	

Statistical analyses

Statistical analysis title	PFS Statistical Analysis
Comparison groups	Arm B: Atezolizumab + Nab-Paclitaxel + Carboplatin v Arm C: Nab-Paclitaxel + Carboplatin
Number of subjects included in analysis	683
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	0.88

Primary: Overall Survival (OS) in the ITT Population	
End point title	Overall Survival (OS) in the ITT Population
End point description:	
OS is defined as the time between the date of randomization and date of death from any cause in the ITT population.	
End point type	Primary
End point timeframe:	
Up to approximately 39 months after first participant enrolled	

End point values	Arm C: Nab-Paclitaxel + Carboplatin	Arm B: Atezolizumab + Nab-Paclitaxel + Carboplatin	Arm A: Atezolizumab + Paclitaxel + Carboplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	340	343	338	
Units: Months				
median (confidence interval 95%)	13.5 (12.2 to 15.1)	14.2 (12.3 to 16.8)	12.6 (11.6 to 14.7)	

Statistical analyses

Statistical analysis title	OS Statistical Analysis
Comparison groups	Arm B: Atezolizumab + Nab-Paclitaxel + Carboplatin v Arm C: Nab-Paclitaxel + Carboplatin
Number of subjects included in analysis	683
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1581
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.05

Secondary: OS in the Tumor Gene Expression (tGE) Population

End point title	OS in the Tumor Gene Expression (tGE) Population

End point description:

End point type	Secondary

End point timeframe:

Up to approximately 39 months after first participant enrolled

End point values	Arm C: Nab-Paclitaxel + Carboplatin	Arm B: Atezolizumab + Nab-Paclitaxel + Carboplatin	Arm A: Atezolizumab + Paclitaxel + Carboplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[1]	0[2]	0[3]	
Units: Month				
median (confidence interval 95%)	(to)	(to)	(to)	

Notes:

[1] - Data will be analyzed at the time of study completion.

[2] - Data will be analyzed at the time of study completion.

[3] - Data will be analyzed at the time of study completion.

Statistical analyses

No statistical analyses for this end point

Secondary: PFS as Determined by the Investigator Using RECIST v1.1 in the tGE Population

End point title	PFS as Determined by the Investigator Using RECIST v1.1 in the tGE Population

End point description:

End point type	Secondary

End point timeframe:

Up to approximately 30 months after first participant enrolled

End point values	Arm C: Nab-Paclitaxel + Carboplatin	Arm B: Atezolizumab + Nab-Paclitaxel + Carboplatin	Arm A: Atezolizumab + Paclitaxel + Carboplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[4]	0[5]	0[6]	
Units: Months				
median (confidence interval 95%)	(to)	(to)	(to)	

Notes:

[4] - Data will be analyzed at the time of study completion.

[5] - Data will be analyzed at the time of study completion.

[6] - Data will be analyzed at the time of study completion.

Statistical analyses

No statistical analyses for this end point

Secondary: PFS as Determined by the Investigator Using RECIST v1.1 in the Tumor Cell (TC) 2/3 or Tumor-Infiltrating Immune Cell (IC) 2/3 Population

End point title	PFS as Determined by the Investigator Using RECIST v1.1 in the Tumor Cell (TC) 2/3 or Tumor-Infiltrating Immune Cell (IC) 2/3 Population

End point description:

End point type	Secondary

End point timeframe:

Up to approximately 30 months after first participant enrolled

End point values	Arm C: Nab-Paclitaxel + Carboplatin	Arm B: Atezolizumab + Nab-Paclitaxel + Carboplatin	Arm A: Atezolizumab + Paclitaxel + Carboplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[7]	0[8]	0[9]	
Units: Months				
median (confidence interval 95%)	(to)	(to)	(to)	

Notes:

[7] - Data will be analyzed at the time of study completion.

[8] - Data will be analyzed at the time of study completion.

[9] - Data will be analyzed at the time of study completion.

Statistical analyses

No statistical analyses for this end point

Secondary: PFS as Determined by the Investigator Using RECIST v1.1 in the

TC1/2/3 or IC1/2/3 Population

End point title	PFS as Determined by the Investigator Using RECIST v1.1 in the TC1/2/3 or IC1/2/3 Population

End point description:

End point type	Secondary

End point timeframe:

Up to approximately 30 months after first participant enrolled

End point values	Arm C: Nab-Paclitaxel + Carboplatin	Arm B: Atezolizumab + Nab-Paclitaxel + Carboplatin	Arm A: Atezolizumab + Paclitaxel + Carboplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[10]	0[11]	0[12]	
Units: Months				
median (confidence interval 95%)	(to)	(to)	(to)	

Notes:

[10] - Data will be analyzed at the time of study completion.

[11] - Data will be analyzed at the time of study completion.

[12] - Data will be analyzed at the time of study completion.

Statistical analyses

No statistical analyses for this end point

Secondary: OS in the TC2/3 or IC2/3 Population

End point title	OS in the TC2/3 or IC2/3 Population

End point description:

End point type	Secondary

End point timeframe:

Up to approximately 39 months after first participant enrolled

End point values	Arm C: Nab-Paclitaxel + Carboplatin	Arm B: Atezolizumab + Nab-Paclitaxel + Carboplatin	Arm A: Atezolizumab + Paclitaxel + Carboplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[13]	0[14]	0[15]	
Units: Months				
median (confidence interval 95%)	(to)	(to)	(to)	

Notes:

[13] - Data will be analyzed at the time of study completion.

[14] - Data will be analyzed at the time of study completion.

[15] - Data will be analyzed at the time of study completion.

Statistical analyses

No statistical analyses for this end point

Secondary: OS in the TC1/2/3 or IC1/2/3 Population

End point title	OS in the TC1/2/3 or IC1/2/3 Population

End point description:

End point type	Secondary

End point timeframe:

Up to approximately 39 months after first participant enrolled

End point values	Arm C: Nab-Paclitaxel + Carboplatin	Arm B: Atezolizumab + Nab-Paclitaxel + Carboplatin	Arm A: Atezolizumab + Paclitaxel + Carboplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[16]	0[17]	0[18]	
Units: Months				
median (confidence interval 95%)	(to)	(to)	(to)	

Notes:

[16] - Data will be analyzed at the time of study completion.

[17] - Data will be analyzed at the time of study completion.

[18] - Data will be analyzed at the time of study completion.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Objective Response as Determined by the Investigator Using RECIST v1.1 in the ITT Population

End point title	Percentage of Participants With Objective Response as Determined by the Investigator Using RECIST v1.1 in the ITT Population

End point description:

End point type	Secondary

End point timeframe:

Up to approximately 30 months after first participant enrolled

End point values	Arm C: Nab-Paclitaxel + Carboplatin	Arm B: Atezolizumab + Nab-Paclitaxel + Carboplatin	Arm A: Atezolizumab + Paclitaxel + Carboplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[19]	0[20]	0[21]	
Units: Percentage				

Notes:

[19] - Data will be analyzed at the time of study completion.

[20] - Data will be analyzed at the time of study completion.
[21] - Data will be analyzed at the time of study completion.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response as Determined by the Investigator Using RECIST v1.1 in the ITT Population

End point title	Duration of Response as Determined by the Investigator Using RECIST v1.1 in the ITT Population

End point description:

End point type	Secondary

End point timeframe:

Up to approximately 30 months after first participant enrolled

End point values	Arm C: Nab-Paclitaxel + Carboplatin	Arm B: Atezolizumab + Nab-Paclitaxel + Carboplatin	Arm A: Atezolizumab + Paclitaxel + Carboplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[22]	0[23]	0[24]	
Units: Months				
median (confidence interval 95%)	(to)	(to)	(to)	

Notes:
[22] - Data will be analyzed at the time of study completion.
[23] - Data will be analyzed at the time of study completion.
[24] - Data will be analyzed at the time of study completion.

Statistical analyses

No statistical analyses for this end point

Secondary: OS at 1 and 2 Years in the ITT Population

End point title	OS at 1 and 2 Years in the ITT Population

End point description:

OS rates at 1 and 2 years is defined as the proportion of participants alive at 1 and 2 years after randomization estimated using Kaplan-Meier (KM) methodology for the ITT population

End point type	Secondary

End point timeframe:

1 and 2 years

End point values	Arm C: Nab-Paclitaxel + Carboplatin	Arm B: Atezolizumab + Nab-Paclitaxel + Carboplatin	Arm A: Atezolizumab + Paclitaxel + Carboplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[25]	0[26]	0[27]	
Units: Months				
number (confidence interval 95%)	(to)	(to)	(to)	

Notes:

[25] - Data will be analyzed at the time of study completion.

[26] - Data will be analyzed at the time of study completion.

[27] - Data will be analyzed at the time of study completion.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Deterioration (TTD) in Patient-reported Lung Cancer Symptoms Using EORTC QLQ-C30 Symptom Subscales in the ITT Population

End point title	Time to Deterioration (TTD) in Patient-reported Lung Cancer Symptoms Using EORTC QLQ-C30 Symptom Subscales in the ITT Population

End point description:

End point type	Secondary

End point timeframe:

Up to approximately 30 months after first participant enrolled

End point values	Arm C: Nab-Paclitaxel + Carboplatin	Arm B: Atezolizumab + Nab-Paclitaxel + Carboplatin	Arm A: Atezolizumab + Paclitaxel + Carboplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[28]	0[29]	0[30]	
Units: Months				
median (confidence interval 95%)	(to)	(to)	(to)	

Notes:

[28] - Data will be analyzed at the time of study completion.

[29] - Data will be analyzed at the time of study completion.

[30] - Data will be analyzed at the time of study completion.

Statistical analyses

No statistical analyses for this end point

Secondary: TTD in Patient-reported Lung Cancer Symptoms Using EORTC QLQ-LC13 Symptom Subscales in the ITT Population

End point title	TTD in Patient-reported Lung Cancer Symptoms Using EORTC QLQ-LC13 Symptom Subscales in the ITT Population

End point description:

End point type	Secondary

End point timeframe:

Up to approximately 30 months after the first participant enrolled

End point values	Arm C: Nab-Paclitaxel + Carboplatin	Arm B: Atezolizumab + Nab-Paclitaxel + Carboplatin	Arm A: Atezolizumab + Paclitaxel + Carboplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[31]	0[32]	0[33]	
Units: Months				
median (confidence interval 95%)	(to)	(to)	(to)	

Notes:

[31] - Data will be analyzed at the time of study completion.

[32] - Data will be analyzed at the time of study completion.

[33] - Data will be analyzed at the time of study completion.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Patient-reported Lung Cancer Symptoms Score using the SILC Scale Symptom Severity Score in the ITT Population

End point title	Change from Baseline in Patient-reported Lung Cancer Symptoms Score using the SILC Scale Symptom Severity Score in the ITT Population

End point description:

End point type	Secondary

End point timeframe:

Baseline up to approximately 30 months after first participant enrolled

End point values	Arm C: Nab-Paclitaxel + Carboplatin	Arm B: Atezolizumab + Nab-Paclitaxel + Carboplatin	Arm A: Atezolizumab + Paclitaxel + Carboplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[34]	0[35]	0[36]	
Units: Months				
median (confidence interval 95%)	(to)	(to)	(to)	

Notes:

[34] - Data will be analyzed at the time of study completion.

[35] - Data will be analyzed at the time of study completion.

[36] - Data will be analyzed at the time of study completion.

Statistical analyses

No statistical analyses for this end point

Secondary: PFS as Determined by the Investigator Using RECIST v1.1 in the ITT

Population (Arm A vs. Arm B)

End point title	PFS as Determined by the Investigator Using RECIST v1.1 in the ITT Population (Arm A vs. Arm B)

End point description:

End point type	Secondary

End point timeframe:

Up to approximately 30 months after first participant enrolled

End point values	Arm C: Nab-Paclitaxel + Carboplatin	Arm B: Atezolizumab + Nab-Paclitaxel + Carboplatin	Arm A: Atezolizumab + Paclitaxel + Carboplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[37]	0[38]	0[39]	
Units: Months				
median (confidence interval 95%)	(to)	(to)	(to)	

Notes:

[37] - Data will be analyzed at the time of study completion.

[38] - Data will be analyzed at the time of study completion.

[39] - Data will be analyzed at the time of study completion.

Statistical analyses

No statistical analyses for this end point

Secondary: OS in the ITT Population (Arm A vs. Arm B)

End point title	OS in the ITT Population (Arm A vs. Arm B)

End point description:

End point type	Secondary

End point timeframe:

Up to approximately 39 months after first participant enrolled

End point values	Arm C: Nab-Paclitaxel + Carboplatin	Arm B: Atezolizumab + Nab-Paclitaxel + Carboplatin	Arm A: Atezolizumab + Paclitaxel + Carboplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[40]	0[41]	0[42]	
Units: Months				
median (confidence interval 95%)	(to)	(to)	(to)	

Notes:

[40] - Data will be analyzed at the time of study completion.

[41] - Data will be analyzed at the time of study completion.

[42] - Data will be analyzed at the time of study completion.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Adverse Events

End point title	Percentage of Participants With Adverse Events

End point description:

End point type	Secondary

End point timeframe:

Up to approximately 39 months after first participant enrolled

End point values	Arm C: Nab-Paclitaxel + Carboplatin	Arm B: Atezolizumab + Nab-Paclitaxel + Carboplatin	Arm A: Atezolizumab + Paclitaxel + Carboplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[43]	0[44]	0[45]	
Units: Percentage				
median (confidence interval 95%)	(to)	(to)	(to)	

Notes:

[43] - Data will be analyzed at the time of study completion.

[44] - Data will be analyzed at the time of study completion.

[45] - Data will be analyzed at the time of study completion.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Anti-therapeutic Antibody (ATA) Response to Atezolizumab

End point title	Percentage of Participants with Anti-therapeutic Antibody (ATA) Response to Atezolizumab

End point description:

The predose samples will be collected on the same day of treatment administration.

End point type	Secondary

End point timeframe:

Predose on Day 1 of Cycles 1-4, 8, 16, every 8 cycle thereafter (up to 39 months), at treatment discontinuation (up to 39 months), and at 120 days after the last dose of atezolizumab (up to approximately 39 months, each cycle is 21 days)

End point values	Arm C: Nab-Paclitaxel + Carboplatin	Arm B: Atezolizumab + Nab-Paclitaxel + Carboplatin	Arm A: Atezolizumab + Paclitaxel + Carboplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[46]	0[47]	0[48]	
Units: Percentage				
geometric mean (confidence interval 95%)	(to)	(to)	(to)	

Notes:

[46] - Data will be analyzed at the time of study completion.

[47] - Data will be analyzed at the time of study completion.

[48] - Data will be analyzed at the time of study completion.

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Serum Atezolizumab Concentration (Cmax)

End point title	Maximum Observed Serum Atezolizumab Concentration (Cmax)

End point description:

The predose samples will be collected on the same day of treatment administration. The infusion duration of atezolizumab will be of 30-60 minutes.

End point type	Secondary

End point timeframe:

Predose on Day 1 of Cycles 1-4, 8, 16, every 8 cycle up to 39 months; 30 minutes postdose on Day 1 of Cycles 1 and 3; at treatment discontinuation (up to 39 months), and at 120 days after last dose of atezolizumab (up to 39 months, each cycle is 21 days)

End point values	Arm C: Nab-Paclitaxel + Carboplatin	Arm B: Atezolizumab + Nab-Paclitaxel + Carboplatin	Arm A: Atezolizumab + Paclitaxel + Carboplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[49]	0[50]	0[51]	
Units: mcg/mL				
geometric mean (standard deviation)	()	()	()	

Notes:

[49] - Data will be analyzed at the time of study completion.

[50] - Data will be analyzed at the time of study completion.

[51] - Data will be analyzed at the time of study completion.

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Observed Serum Atezolizumab Concentration (Cmin)

End point title	Minimum Observed Serum Atezolizumab Concentration (Cmin)

End point description:

The predose samples will be collected on the same day of treatment administration.

End point type	Secondary

End point timeframe:

Predose on Day 1 of Cycles 1-4, 8, 16, every 8 cycle thereafter (up to 39 months), at treatment discontinuation (up to 39 months), and at 120 days after the last dose of atezolizumab (up to approximately 39 months, each cycle is 21 days)

End point values	Arm C: Nab-Paclitaxel + Carboplatin	Arm B: Atezolizumab + Nab-Paclitaxel + Carboplatin	Arm A: Atezolizumab + Paclitaxel + Carboplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[52]	0[53]	0[54]	
Units: mcg/mL				
geometric mean (standard deviation)	()	()	()	

Notes:

[52] - Data will be analyzed at the time of study completion.

[53] - Data will be analyzed at the time of study completion.

[54] - Data will be analyzed at the time of study completion.

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations for Paclitaxel

End point title	Plasma Concentrations for Paclitaxel

End point description:

End point type	Secondary

End point timeframe:

Prior to infusion (within same day of treatment administration), 5-10 minutes before the end of infusion, and 1 hour after the end of infusion (infusion duration 180 minutes) on Day 1 of Cycles 1 and 3 (each cycle is 21 days)

End point values	Arm C: Nab-Paclitaxel + Carboplatin	Arm B: Atezolizumab + Nab-Paclitaxel + Carboplatin	Arm A: Atezolizumab + Paclitaxel + Carboplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[55]	0[56]	0[57]	
Units: mcg/mL				
geometric mean (standard deviation)	()	()	()	

Notes:

[55] - Data will be analyzed at the time of study completion.

[56] - Data will be analyzed at the time of study completion.

[57] - Data will be analyzed at the time of study completion.

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations for Nab-Paclitaxel

End point title	Plasma Concentrations for Nab-Paclitaxel

End point description:

End point type	Secondary

End point timeframe:

Prior to infusion (within same day of treatment administration), 5-10 minutes before the end of infusion, and 1 hour after the end of infusion (infusion duration 30 minutes) on Day 1 of Cycles 1 and 3 (each

cycle is 21 days)

End point values	Arm C: Nab-Paclitaxel + Carboplatin	Arm B: Atezolizumab + Nab-Paclitaxel + Carboplatin	Arm A: Atezolizumab + Paclitaxel + Carboplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[58]	0[59]	0[60]	
Units: mcg/mL				
geometric mean (standard deviation)	()	()	()	

Notes:

[58] - Data will be analyzed at the time of study completion.

[59] - Data will be analyzed at the time of study completion.

[60] - Data will be analyzed at the time of study completion.

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations for Carboplatin

End point title	Plasma Concentrations for Carboplatin

End point description:

End point type	Secondary

End point timeframe:

Prior to infusion (within same day of treatment administration), 5-10 minutes before the end of infusion, and 1 hour after the end of infusion (infusion duration 15 to 30 minutes) on Day 1 of Cycles 1 and 3 (each cycle is 21 days)

End point values	Arm C: Nab-Paclitaxel + Carboplatin	Arm B: Atezolizumab + Nab-Paclitaxel + Carboplatin	Arm A: Atezolizumab + Paclitaxel + Carboplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[61]	0[62]	0[63]	
Units: mcg/mL				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[61] - Data will be analyzed at the time of study completion.

[62] - Data will be analyzed at the time of study completion.

[63] - Data will be analyzed at the time of study completion.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first study drug administration to the data cutoff date: 3 October 2018.

Adverse event reporting additional description:

Safety-evaluable population included all participants who received at least one dose of any study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MeDRA Version 21.1
Dictionary version	21.1

Reporting groups

Reporting group title	Arm C: Nab-Paclitaxel + Carboplatin

Reporting group description:

The induction phase of the study consisted of four or six cycles; carboplatin was administered on Day 1 of each 21-day cycle, nab-paclitaxel was administered on Days 1, 8, and 15 of each 21-day cycle. The Day 1 order of drug administration was as follows: nab-paclitaxel, then carboplatin. Participants who experienced disease progression at any time during the induction phase discontinued all study treatment. In the maintenance phase, participants received best supportive care.

Reporting group title	Arm B: Atezolizumab + Nab-Paclitaxel + Carboplatin

Reporting group description:

The induction phase of the study consisted of four or six cycles; atezolizumab and carboplatin were administered on Day 1 of each 21-day cycle. Nab-Paclitaxel was administered on Days 1, 8, and 15 of each 21-day cycle. The Day 1 order of drug administration was as follows: atezolizumab, then nab-paclitaxel, then carboplatin. Participants who experienced no further clinical benefit at any time during the induction phase discontinued all study treatments. In the absence of the above criteria, after the 4- or 6-cycle induction phase, participants began maintenance therapy with atezolizumab. Atezolizumab was continued as long as there was clinical benefit to the participant.

Reporting group title	Arm A: Atezolizumab + Paclitaxel + Carboplatin

Reporting group description:

The induction phase of the study consisted of four or six cycles; atezolizumab, paclitaxel, and carboplatin were administered on Day 1 of each 21-day cycle. The Day 1 order of drug administration was as follows: atezolizumab, then paclitaxel, then carboplatin. Participants who experienced no further clinical benefit at any time during the induction phase discontinued all study treatments. In the absence of the above criteria, after the 4- or 6-cycle induction phase, participants began maintenance therapy with atezolizumab. Atezolizumab was continued as long as there was clinical benefit to the participant.

Serious adverse events	Arm C: Nab-Paclitaxel + Carboplatin	Arm B: Atezolizumab + Nab-Paclitaxel + Carboplatin	Arm A: Atezolizumab + Paclitaxel + Carboplatin
Total subjects affected by serious adverse events			
subjects affected / exposed	96 / 334 (28.74%)	160 / 334 (47.90%)	143 / 332 (43.07%)
number of deaths (all causes)	242	221	233
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign Salivary Gland Neoplasm			

subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon Cancer			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder Adenocarcinoma			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected Neoplasm			
subjects affected / exposed	1 / 334 (0.30%)	0 / 334 (0.00%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Prostate Cancer			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour Embolism			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Vascular disorders			
Deep Vein Thrombosis			
subjects affected / exposed	1 / 334 (0.30%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Haemodynamic Instability			

subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hypotension			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic Hypotension			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral Arterial Occlusive Disease			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superior Vena Cava Syndrome			
subjects affected / exposed	0 / 334 (0.00%)	2 / 334 (0.60%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Surgical and medical procedures			
Therapeutic Embolisation			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 334 (0.30%)	0 / 334 (0.00%)	2 / 332 (0.60%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest Pain			
subjects affected / exposed	2 / 334 (0.60%)	0 / 334 (0.00%)	3 / 332 (0.90%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Death			
subjects affected / exposed	0 / 334 (0.00%)	7 / 334 (2.10%)	2 / 332 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 7	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 7	1 / 2
Fatigue			
subjects affected / exposed	0 / 334 (0.00%)	3 / 334 (0.90%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	2 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gait Disturbance			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	1 / 334 (0.30%)	2 / 334 (0.60%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucosal Inflammation			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-Cardiac Chest Pain			
subjects affected / exposed	1 / 334 (0.30%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Performance Status Decreased			

subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	5 / 334 (1.50%)	5 / 334 (1.50%)	5 / 332 (1.51%)
occurrences causally related to treatment / all	3 / 6	0 / 5	3 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic Reaction			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	2 / 332 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug Hypersensitivity			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	2 / 332 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemophagocytic Lymphohistiocytosis			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 334 (0.00%)	2 / 334 (0.60%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Atelectasis			

subjects affected / exposed	1 / 334 (0.30%)	0 / 334 (0.00%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchial Haemorrhage			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	3 / 334 (0.90%)	6 / 334 (1.80%)	10 / 332 (3.01%)
occurrences causally related to treatment / all	0 / 3	0 / 6	1 / 14
deaths causally related to treatment / all	0 / 1	0 / 3	0 / 1
Cough			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	2 / 332 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diaphragmatic Paralysis			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	3 / 334 (0.90%)	6 / 334 (1.80%)	6 / 332 (1.81%)
occurrences causally related to treatment / all	0 / 4	1 / 7	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Dyspnoea at Rest			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea Exertional			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Emphysema			

subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	1 / 334 (0.30%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	2 / 334 (0.60%)	5 / 334 (1.50%)	5 / 332 (1.51%)
occurrences causally related to treatment / all	0 / 2	0 / 5	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 1	1 / 3
Hypoxia			
subjects affected / exposed	1 / 334 (0.30%)	1 / 334 (0.30%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial Lung Disease			
subjects affected / exposed	1 / 334 (0.30%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal Haemorrhage			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung Consolidation			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung Disorder			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paranasal Cyst			

subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural Effusion			
subjects affected / exposed	0 / 334 (0.00%)	2 / 334 (0.60%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia Aspiration			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	2 / 334 (0.60%)	10 / 334 (2.99%)	11 / 332 (3.31%)
occurrences causally related to treatment / all	2 / 2	10 / 10	11 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Pneumothorax			
subjects affected / exposed	3 / 334 (0.90%)	3 / 334 (0.90%)	2 / 332 (0.60%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax Spontaneous			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Embolism			
subjects affected / exposed	3 / 334 (0.90%)	3 / 334 (0.90%)	7 / 332 (2.11%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 7
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 4
Pulmonary Oedema			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	2 / 332 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory Failure			

subjects affected / exposed	3 / 334 (0.90%)	2 / 334 (0.60%)	3 / 332 (0.90%)
occurrences causally related to treatment / all	0 / 3	0 / 2	2 / 4
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Psychiatric disorders			
Completed Suicide			
subjects affected / exposed	0 / 334 (0.00%)	2 / 334 (0.60%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Confusional State			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	1 / 334 (0.30%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucination			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental Status Changes			
subjects affected / exposed	0 / 334 (0.00%)	2 / 334 (0.60%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal Ideation			
subjects affected / exposed	1 / 334 (0.30%)	0 / 334 (0.00%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device Dislocation			
subjects affected / exposed	1 / 334 (0.30%)	0 / 334 (0.00%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			

Blood Bilirubin Increased			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood Creatinine Increased			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood Lactic Acid Increased			
subjects affected / exposed	1 / 334 (0.30%)	0 / 334 (0.00%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General Physical Condition Abnormal			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver Function Test Abnormal			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil Count Decreased			
subjects affected / exposed	1 / 334 (0.30%)	1 / 334 (0.30%)	3 / 332 (0.90%)
occurrences causally related to treatment / all	1 / 1	1 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet Count Decreased			
subjects affected / exposed	2 / 334 (0.60%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight Decreased			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			

Alcohol Poisoning			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest Injury			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fermur Fracture			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip Fracture			
subjects affected / exposed	0 / 334 (0.00%)	2 / 334 (0.60%)	2 / 332 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Humerus Fracture			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion Related Reaction			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	2 / 332 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periorbital Haematoma			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiation Oesophagitis			

subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiation Pneumonitis			
subjects affected / exposed	0 / 334 (0.00%)	2 / 334 (0.60%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib Fracture			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin Laceration			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural Haematoma			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracic Vertebral Fracture			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to Various Agents			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Tracheo-Oesophageal Fistula			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

Acute Myocardial Infarction			
subjects affected / exposed	1 / 334 (0.30%)	2 / 334 (0.60%)	2 / 332 (0.60%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	1 / 334 (0.30%)	0 / 334 (0.00%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial Fibrillation			
subjects affected / exposed	3 / 334 (0.90%)	2 / 334 (0.60%)	6 / 332 (1.81%)
occurrences causally related to treatment / all	0 / 3	0 / 3	2 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial Flutter			
subjects affected / exposed	1 / 334 (0.30%)	0 / 334 (0.00%)	5 / 332 (1.51%)
occurrences causally related to treatment / all	1 / 1	0 / 0	3 / 5
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Atrial Thrombosis			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	1 / 334 (0.30%)	0 / 334 (0.00%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac Arrest			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	2 / 332 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 2
Cardiac Failure			
subjects affected / exposed	1 / 334 (0.30%)	2 / 334 (0.60%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac Failure Acute			

subjects affected / exposed	2 / 334 (0.60%)	0 / 334 (0.00%)	2 / 332 (0.60%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 2	0 / 0	1 / 1
Cardiac Tamponade			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-Respiratory Arrest			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Coronary Artery Stenosis			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left Ventricular Dysfunction			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial Infarction			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pericardial Effusion			
subjects affected / exposed	0 / 334 (0.00%)	4 / 334 (1.20%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus Tachycardia			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			

subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Brain Oedema			
subjects affected / exposed	1 / 334 (0.30%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral Ischaemia			
subjects affected / exposed	1 / 334 (0.30%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular Accident			
subjects affected / exposed	1 / 334 (0.30%)	0 / 334 (0.00%)	4 / 332 (1.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Depressed Level of Consciousness			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 334 (0.30%)	0 / 334 (0.00%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolic Stroke			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Guillain-Barre Syndrome			

subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Hemiplegia			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperaesthesia			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotonia			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic Stroke			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Motor Dysfunction			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myxoedema Coma			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			

subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal Cord Compression			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 334 (0.00%)	2 / 334 (0.60%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 334 (0.90%)	7 / 334 (2.10%)	6 / 332 (1.81%)
occurrences causally related to treatment / all	2 / 3	6 / 7	5 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ferbrile Neutropenia			
subjects affected / exposed	5 / 334 (1.50%)	13 / 334 (3.89%)	16 / 332 (4.82%)
occurrences causally related to treatment / all	5 / 5	15 / 15	15 / 16
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemolysis			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	3 / 334 (0.90%)	3 / 334 (0.90%)	2 / 332 (0.60%)
occurrences causally related to treatment / all	2 / 3	3 / 3	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	2 / 334 (0.60%)	0 / 334 (0.00%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			

subjects affected / exposed	1 / 334 (0.30%)	2 / 334 (0.60%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	1 / 1	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal Detachment			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	1 / 334 (0.30%)	1 / 334 (0.30%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Pain Upper			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal Haemorrhage			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 334 (0.00%)	3 / 334 (0.90%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	3 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 334 (0.30%)	0 / 334 (0.00%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	4 / 334 (1.20%)	6 / 334 (1.80%)	3 / 332 (0.90%)
occurrences causally related to treatment / all	4 / 5	4 / 6	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal Perforation			

subjects affected / exposed	1 / 334 (0.30%)	0 / 334 (0.00%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	2 / 332 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Gastritis			
subjects affected / exposed	1 / 334 (0.30%)	0 / 334 (0.00%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal Haemorrhage			
subjects affected / exposed	2 / 334 (0.60%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Gastrointestinal Necrosis			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal Perforation			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal Toxicity			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal Hernia			

subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal Perforation			
subjects affected / exposed	1 / 334 (0.30%)	0 / 334 (0.00%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large Intestine Perforation			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nausea			
subjects affected / exposed	1 / 334 (0.30%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis Chronic			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal Haemorrhage			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small Intestinal Obstruction			

subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper Gastrointestinal Haemorrhage			
subjects affected / exposed	1 / 334 (0.30%)	0 / 334 (0.00%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 334 (0.30%)	1 / 334 (0.30%)	2 / 332 (0.60%)
occurrences causally related to treatment / all	0 / 1	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Autoimmune Hepatitis			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile Duct Stone			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	1 / 334 (0.30%)	1 / 334 (0.30%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis Acute			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-Induced Liver Injury			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic Function Abnormal			

subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Hepatitis			
subjects affected / exposed	1 / 334 (0.30%)	0 / 334 (0.00%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis Toxic			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-Mediated Hepatitis			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis Acneiform			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erythema Multiforme			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	1 / 334 (0.30%)	4 / 334 (1.20%)	2 / 332 (0.60%)
occurrences causally related to treatment / all	0 / 1	0 / 4	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			

subjects affected / exposed	1 / 334 (0.30%)	0 / 334 (0.00%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Retention			
subjects affected / exposed	1 / 334 (0.30%)	2 / 334 (0.60%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenal Insufficiency			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperthyroidism			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypopituitarism			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	5 / 332 (1.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flank Pain			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal Chest Pain			
subjects affected / exposed	1 / 334 (0.30%)	0 / 334 (0.00%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal Pain			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological Fracture			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyarthritis			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polymyositis			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal Infection			
subjects affected / exposed	1 / 334 (0.30%)	0 / 334 (0.00%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 334 (0.30%)	3 / 334 (0.90%)	5 / 332 (1.51%)
occurrences causally related to treatment / all	0 / 1	0 / 3	2 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			

subjects affected / exposed	1 / 334 (0.30%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium Difficle Infection			
subjects affected / exposed	0 / 334 (0.00%)	2 / 334 (0.60%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic Abscess			
subjects affected / exposed	1 / 334 (0.30%)	0 / 334 (0.00%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device Related Infection			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis Infection			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 334 (0.00%)	2 / 334 (0.60%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis B			
subjects affected / exposed	1 / 334 (0.30%)	0 / 334 (0.00%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected Dermal Cyst			

subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection Exacerbation of Chronic Obstructive Ariways Disease			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Lower Respiratory Tract Infection			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung Abscess			
subjects affected / exposed	1 / 334 (0.30%)	0 / 334 (0.00%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung Infection			
subjects affected / exposed	7 / 334 (2.10%)	1 / 334 (0.30%)	5 / 332 (1.51%)
occurrences causally related to treatment / all	3 / 7	0 / 1	2 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Meningitis			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural Infection			

subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	14 / 334 (4.19%)	30 / 334 (8.98%)	25 / 332 (7.53%)
occurrences causally related to treatment / all	6 / 14	6 / 34	5 / 27
deaths causally related to treatment / all	1 / 1	2 / 6	1 / 3
Pneumonia Bacterial			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia Haemophilus			
subjects affected / exposed	1 / 334 (0.30%)	0 / 334 (0.00%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia Staphylococcal			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia Streptococcal			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomonal Sepsis			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Sepsis			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory Tract Infection			

subjects affected / exposed	3 / 334 (0.90%)	2 / 334 (0.60%)	2 / 332 (0.60%)
occurrences causally related to treatment / all	0 / 3	0 / 3	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	6 / 334 (1.80%)	5 / 334 (1.50%)	9 / 332 (2.71%)
occurrences causally related to treatment / all	2 / 6	1 / 5	2 / 10
deaths causally related to treatment / all	0 / 2	0 / 2	1 / 3
Septic Shock			
subjects affected / exposed	1 / 334 (0.30%)	3 / 334 (0.90%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	1 / 1	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	1 / 2	0 / 1
Sinusitis			
subjects affected / exposed	1 / 334 (0.30%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatococcal Infection			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 334 (0.00%)	2 / 334 (0.60%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Tract Infection			
subjects affected / exposed	3 / 334 (0.90%)	2 / 334 (0.60%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Tract Infection Staphylococcal			
subjects affected / exposed	1 / 334 (0.30%)	0 / 334 (0.00%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			

subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	2 / 334 (0.60%)	3 / 334 (0.90%)	4 / 332 (1.20%)
occurrences causally related to treatment / all	2 / 2	1 / 3	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes Mellitus			
subjects affected / exposed	0 / 334 (0.00%)	0 / 334 (0.00%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to Thrive			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	2 / 334 (0.60%)	1 / 334 (0.30%)	2 / 332 (0.60%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			

subjects affected / exposed	0 / 334 (0.00%)	2 / 334 (0.60%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypomagnesaemia			
subjects affected / exposed	0 / 334 (0.00%)	2 / 334 (0.60%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	3 / 334 (0.90%)	2 / 334 (0.60%)	1 / 332 (0.30%)
occurrences causally related to treatment / all	1 / 3	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 Diabetes Mellitus			
subjects affected / exposed	0 / 334 (0.00%)	1 / 334 (0.30%)	0 / 332 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Arm C: Nab-Paclitaxel + Carboplatin	Arm B: Atezolizumab + Nab-Paclitaxel + Carboplatin	Arm A: Atezolizumab + Paclitaxel + Carboplatin
Total subjects affected by non-serious adverse events			
subjects affected / exposed	315 / 334 (94.31%)	325 / 334 (97.31%)	315 / 332 (94.88%)
Vascular disorders			
Hypotension			
subjects affected / exposed	11 / 334 (3.29%)	18 / 334 (5.39%)	22 / 332 (6.63%)
occurrences (all)	17	25	25
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	66 / 334 (19.76%)	58 / 334 (17.37%)	77 / 332 (23.19%)
occurrences (all)	85	79	99
Chest Pain			
subjects affected / exposed	18 / 334 (5.39%)	24 / 334 (7.19%)	27 / 332 (8.13%)
occurrences (all)	19	29	29
Fatigue			

subjects affected / exposed	88 / 334 (26.35%)	103 / 334 (30.84%)	95 / 332 (28.61%)
occurrences (all)	101	127	109
Malaise			
subjects affected / exposed	16 / 334 (4.79%)	17 / 334 (5.09%)	10 / 332 (3.01%)
occurrences (all)	24	25	14
Mucosal Inflammation			
subjects affected / exposed	9 / 334 (2.69%)	16 / 334 (4.79%)	17 / 332 (5.12%)
occurrences (all)	11	23	17
Oedema Peripheral			
subjects affected / exposed	22 / 334 (6.59%)	26 / 334 (7.78%)	22 / 332 (6.63%)
occurrences (all)	25	31	27
Pyrexia			
subjects affected / exposed	34 / 334 (10.18%)	44 / 334 (13.17%)	44 / 332 (13.25%)
occurrences (all)	42	65	63
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	51 / 334 (15.27%)	59 / 334 (17.66%)	59 / 332 (17.77%)
occurrences (all)	61	74	67
Dysphonia			
subjects affected / exposed	11 / 334 (3.29%)	18 / 334 (5.39%)	14 / 332 (4.22%)
occurrences (all)	11	18	14
Dyspnoea			
subjects affected / exposed	57 / 334 (17.07%)	66 / 334 (19.76%)	61 / 332 (18.37%)
occurrences (all)	65	94	72
Epistaxis			
subjects affected / exposed	37 / 334 (11.08%)	34 / 334 (10.18%)	8 / 332 (2.41%)
occurrences (all)	43	37	9
Haemoptysis			
subjects affected / exposed	18 / 334 (5.39%)	18 / 334 (5.39%)	18 / 332 (5.42%)
occurrences (all)	27	28	20
Psychiatric disorders			
Insomnia			
subjects affected / exposed	27 / 334 (8.08%)	30 / 334 (8.98%)	29 / 332 (8.73%)
occurrences (all)	28	34	31
Investigations			

Alanine Aminotransferase Increased			
subjects affected / exposed	18 / 334 (5.39%)	40 / 334 (11.98%)	33 / 332 (9.94%)
occurrences (all)	23	61	53
Aspartate Aminotransferase Increased			
subjects affected / exposed	17 / 334 (5.09%)	34 / 334 (10.18%)	30 / 332 (9.04%)
occurrences (all)	27	60	50
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	8 / 334 (2.40%)	13 / 334 (3.89%)	25 / 332 (7.53%)
occurrences (all)	8	14	33
Blood Creatinine Increased			
subjects affected / exposed	3 / 334 (0.90%)	23 / 334 (6.89%)	13 / 332 (3.92%)
occurrences (all)	4	26	13
Neutrophil Count Decreased			
subjects affected / exposed	65 / 334 (19.46%)	60 / 334 (17.96%)	17 / 332 (5.12%)
occurrences (all)	145	132	24
Platelet Count Decreased			
subjects affected / exposed	59 / 334 (17.66%)	59 / 334 (17.66%)	40 / 332 (12.05%)
occurrences (all)	110	125	64
Weight Decreased			
subjects affected / exposed	14 / 334 (4.19%)	29 / 334 (8.68%)	20 / 332 (6.02%)
occurrences (all)	14	34	21
White Blood Cell Count Decreased			
subjects affected / exposed	36 / 334 (10.78%)	32 / 334 (9.58%)	12 / 332 (3.61%)
occurrences (all)	68	64	19
Nervous system disorders			
Dizziness			
subjects affected / exposed	32 / 334 (9.58%)	31 / 334 (9.28%)	31 / 332 (9.34%)
occurrences (all)	41	36	33
Dysgeusia			
subjects affected / exposed	30 / 334 (8.98%)	31 / 334 (9.28%)	16 / 332 (4.82%)
occurrences (all)	31	35	16
Headache			
subjects affected / exposed	18 / 334 (5.39%)	30 / 334 (8.98%)	37 / 332 (11.14%)
occurrences (all)	26	35	43
Neuropathy Peripherial			

subjects affected / exposed	35 / 334 (10.48%)	34 / 334 (10.18%)	66 / 332 (19.88%)
occurrences (all)	38	39	73
Paraesthesia			
subjects affected / exposed	15 / 334 (4.49%)	16 / 334 (4.79%)	26 / 332 (7.83%)
occurrences (all)	16	17	31
Peripheral Sensory Neuropathy			
subjects affected / exposed	30 / 334 (8.98%)	48 / 334 (14.37%)	55 / 332 (16.57%)
occurrences (all)	35	54	68
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	193 / 334 (57.78%)	186 / 334 (55.69%)	128 / 332 (38.55%)
occurrences (all)	244	250	154
Leukopenia			
subjects affected / exposed	34 / 334 (10.18%)	42 / 334 (12.57%)	8 / 332 (2.41%)
occurrences (all)	54	86	8
Neutropenia			
subjects affected / exposed	122 / 334 (36.53%)	121 / 334 (36.23%)	42 / 332 (12.65%)
occurrences (all)	212	260	59
Thrombocytopenia			
subjects affected / exposed	92 / 334 (27.54%)	90 / 334 (26.95%)	46 / 332 (13.86%)
occurrences (all)	170	161	66
Gastrointestinal disorders			
Abdominal Pain Upper			
subjects affected / exposed	17 / 334 (5.09%)	12 / 334 (3.59%)	12 / 332 (3.61%)
occurrences (all)	17	15	15
Constipation			
subjects affected / exposed	72 / 334 (21.56%)	101 / 334 (30.24%)	75 / 332 (22.59%)
occurrences (all)	84	124	93
Diarrhoea			
subjects affected / exposed	77 / 334 (23.05%)	88 / 334 (26.35%)	93 / 332 (28.01%)
occurrences (all)	107	128	114
Nausea			
subjects affected / exposed	96 / 334 (28.74%)	129 / 334 (38.62%)	93 / 332 (28.01%)
occurrences (all)	136	197	133
Stomatitis			

subjects affected / exposed	15 / 334 (4.49%)	22 / 334 (6.59%)	19 / 332 (5.72%)
occurrences (all)	17	26	22
Vomitting			
subjects affected / exposed	48 / 334 (14.37%)	63 / 334 (18.86%)	49 / 332 (14.76%)
occurrences (all)	59	78	62
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	102 / 334 (30.54%)	113 / 334 (33.83%)	130 / 332 (39.16%)
occurrences (all)	103	113	134
Dry Skin			
subjects affected / exposed	5 / 334 (1.50%)	17 / 334 (5.09%)	13 / 332 (3.92%)
occurrences (all)	5	18	14
Pruritus			
subjects affected / exposed	12 / 334 (3.59%)	20 / 334 (5.99%)	32 / 332 (9.64%)
occurrences (all)	13	29	42
Rash			
subjects affected / exposed	18 / 334 (5.39%)	42 / 334 (12.57%)	41 / 332 (12.35%)
occurrences (all)	19	47	53
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	2 / 334 (0.60%)	31 / 334 (9.28%)	25 / 332 (7.53%)
occurrences (all)	2	36	26
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	22 / 334 (6.59%)	38 / 334 (11.38%)	61 / 332 (18.37%)
occurrences (all)	25	51	80
Back Pain			
subjects affected / exposed	16 / 334 (4.79%)	36 / 334 (10.78%)	31 / 332 (9.34%)
occurrences (all)	17	40	35
Bone Pain			
subjects affected / exposed	3 / 334 (0.90%)	9 / 334 (2.69%)	22 / 332 (6.63%)
occurrences (all)	3	11	34
Musculoskeletal Pain			
subjects affected / exposed	13 / 334 (3.89%)	21 / 334 (6.29%)	26 / 332 (7.83%)
occurrences (all)	16	28	32
Myalgia			

subjects affected / exposed	19 / 334 (5.69%)	22 / 334 (6.59%)	43 / 332 (12.95%)
occurrences (all)	24	23	62
Pain in Extremity			
subjects affected / exposed	17 / 334 (5.09%)	31 / 334 (9.28%)	35 / 332 (10.54%)
occurrences (all)	17	34	46
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	8 / 334 (2.40%)	17 / 334 (5.09%)	17 / 332 (5.12%)
occurrences (all)	10	18	27
Pneumonia			
subjects affected / exposed	13 / 334 (3.89%)	17 / 334 (5.09%)	14 / 332 (4.22%)
occurrences (all)	14	18	14
Respiratory Tract Infection			
subjects affected / exposed	6 / 334 (1.80%)	9 / 334 (2.69%)	22 / 332 (6.63%)
occurrences (all)	6	13	34
Upper Respiratory Tract Infection			
subjects affected / exposed	6 / 334 (1.80%)	17 / 334 (5.09%)	15 / 332 (4.52%)
occurrences (all)	6	23	23
Urinary Tract Infection			
subjects affected / exposed	14 / 334 (4.19%)	25 / 334 (7.49%)	16 / 332 (4.82%)
occurrences (all)	18	39	21
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	84 / 334 (25.15%)	83 / 334 (24.85%)	92 / 332 (27.71%)
occurrences (all)	98	107	106
Dehydration			
subjects affected / exposed	11 / 334 (3.29%)	23 / 334 (6.89%)	20 / 332 (6.02%)
occurrences (all)	15	33	30
Hyperglycaemia			
subjects affected / exposed	17 / 334 (5.09%)	18 / 334 (5.39%)	25 / 332 (7.53%)
occurrences (all)	19	24	28
Hypokalaemia			
subjects affected / exposed	23 / 334 (6.89%)	28 / 334 (8.38%)	24 / 332 (7.23%)
occurrences (all)	28	35	30
Hypomagnesaemia			

subjects affected / exposed occurrences (all)	38 / 334 (11.38%) 56	53 / 334 (15.87%) 78	35 / 332 (10.54%) 40

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 March 2015	Protocol was amended to clarify the inclusion criterion on contraception. In addition, reporting for serious adverse events and adverse events of special interest has been extended to 90 days after last dose of study treatment or until intitation of a new anticancer therapy, whichever occurs first.
14 August 2015	Protocol was amended to update the contraception requirements in the inclusion and exclusion criteria and the pregnancy-reporting information to be consistent with safety information for nab-paclitaxel. The study inclusion criteria have been modified, on the basis of an expanding safety database, to allow for patients with treated, asymptomatic cerebellar metastases to be enrolled provided specific criteria are met. The exclusion criteria for history of autoimmune disease has been broadened, on the basis of an expanding safety database, to allow for patients with eczema, psoriasis, or lichen simplex chronicus of vitiligo with dermatologic manifestations only to be permitted provided that they meet the specific conditions. The study exclusion criteria regarding treatment with systemic immunostimulatory agents within 6 weeks or 5 half-lives of the drug (whichever is shorter) prior to randomization has been modified to 4 weeks prior to randomization for consistency with more recent atezolizumab protocols. The exclusion criterion specifying that patients with a history of allergic reaction to intravenous contrast that requires steroid pretreatment should have baseline and subsequent tumor assessments performed via magnetic resonance imaging (MRI) has been removed.
11 November 2015	Protocol was amended to clarify that a wash-out period of at least 4 weeks or five half-lives, whichever is longer, of any systemic immunomodulatory agent is required prior to enrollment.
15 June 2016	Protocol was amended to add a co-primary endpoint of overall survival (OS) to the progression-free survival (PFS) primary endpoint. A secondary efficacy objective and outcome measure was added to evaluate the efficacy of atezolizumab + carboplatin + nab-paclitaxel compared with carboplatin + nab-paclitaxel as measured by investigator-assessed time to response (TTR) according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) for both the ITT and PD-L1−selected populations. The inclusion criteria was modified to specify that patients who have received prior radiotherapy with curative intent must be treatment-free for at least a 6-month interval prior to randomization. Based on the half-life of atezolizumab of 27 days, the language regarding length of female patient contraception and follow-up of pregnancy reporting has been revised from 90 days to 5 months. The contraception requirements for male patients and pregnancy-reporting requirements for female partners of male patients who receive atezolizumab have been updated on the basis of the safety information for atezolizumab.
01 March 2017	Protocol was amended to include changes in the primary analysis populations fr the co-primary endpoints of progression-free survival (PFS) and overall survival (OS). OS will be analyzed in the intent-to-treat (ITT) population, PFS will be analyzed in the ITT population with a defined level of expression of a PD-L1 and T-effector gene signature in tumor tissue as determined by an RNA-based assay.
24 October 2018	Protocol was amended to include correction to the end of study definition. This correction ensures that the study continues until last patient, last visit or until the Sponsor terminates the stud. Inclusion criterion has been modified to address female contraception to specify when women must refrain from donating eggs.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported