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

Summary

EudraCT number	2014-003206-32
Trial protocol	DE BE IT FR ES
Global end of trial date	

Results information

Result version number	v1
This version publication date	29 March 2019
First version publication date	29 March 2019

Trial information

Trial identification

Sponsor protocol code	GO29537

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02367781
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, lobal.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	15 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 March 2018
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

This randomized Phase III, multicenter, open-label study is designed to evaluate the safety and efficacy of atezolizumab (an engineered anti-programmed death-ligand 1 [PD-L1] antibody) in combination with carboplatin+nab-paclitaxel compared with treatment with carboplatin+nab-paclitaxel in chemotherapy-naive subjects with Stage IV non-squamous 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	16 April 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	Israel: 35
Country: Number of subjects enrolled	Belgium: 21
Country: Number of subjects enrolled	Germany: 132
Country: Number of subjects enrolled	Spain: 71
Country: Number of subjects enrolled	France: 45
Country: Number of subjects enrolled	Italy: 52
Country: Number of subjects enrolled	Canada: 52
Country: Number of subjects enrolled	United States: 315
Worldwide total number of subjects	723
EEA total number of subjects	321

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)	362
From 65 to 84 years	358
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects in this study included: histologically or cytologically confirmed, Stage IV non-squamous NSCLC; and no prior treatment for Stage IV non-squamous 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 A (Atezolizumab+Nab-Paclitaxel+Carboplatin)

Arm description:

Subjects will receive intravenous (IV) infusion of atezolizumab and carboplatin on Day 1 of each 21-day cycle, and nab-paclitaxel on Days 1, 8, and 15 of each 21-day cycle for 4 or 6 cycles or until loss of clinical benefit whichever occurs first during induction treatment phase. Subjects will receive IV infusion of atezolizumab during maintenance treatment phase until loss of clinical benefit.

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

Dosage and administration details:

Atezolizumab will be administered as IV infusion at a dose of 1200 milligrams (mg) 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 will be administered as IV infusion at a dose of 100 milligrams per square meter (mg/m^2) on Days 1, 8, and 15 of each 21-day cycle.

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

Dosage and administration details:

Carboplatin will be administered at area under the concentration curve (AUC) 6 milligrams per milliliter per minute (mg/mL/min) on Day 1 of each 21-day cycle.

Arm title	Arm B (Nab-Paclitaxel+Carboplatin)

Arm description:

Subjects will receive IV infusion of carboplatin on Day 1 and nab-paclitaxel on Days 1, 8, and 15 of each 21-day cycle for 4 or 6 cycles or until disease progression whichever occurs first during induction treatment phase. Subjects will receive best supportive care during maintenance treatment phase.

Switch maintenance to pemetrexed is also permitted. Subjects who were consented prior to approval of protocol Version 5 will be given the option to cross over to receive atezolizumab as monotherapy until disease progression.

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 will be administered as IV infusion at a dose of 100 milligrams per square meter (mg/m^2) on Days 1, 8, and 15 of each 21-day cycle.

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

Dosage and administration details:

Carboplatin will be administered at area under the concentration curve (AUC) 6 milligrams per milliliter per minute (mg/mL/min) on Day 1 of each 21-day cycle.

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

Dosage and administration details:

Switch maintenance to pemetrexed can be administered within 6 weeks of Day 1 of the last induction cycle.

Number of subjects in period 1	Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin)	Arm B (Nab-Paclitaxel+Carboplatin)
Started	483	240
Completed	0	0
Not completed	483	240
Adverse event, serious fatal	240	136
Prolonged Hospitalization	1	-
Consent withdrawn by subject	19	10
Physician decision	1	-
Non-Compliance	1	-
On-going in study	214	88
Lost to follow-up	-	1
Death Prior to First Dose	1	-
Administrative-Change Facility	1	-
Randomized in Error	5	4
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin)
Reporting group description:	
Subjects will receive intravenous (IV) infusion of atezolizumab and carboplatin on Day 1 of each 21-day cycle, and nab-paclitaxel on Days 1, 8, and 15 of each 21-day cycle for 4 or 6 cycles or until loss of clinical benefit whichever occurs first during induction treatment phase. Subjects will receive IV infusion of atezolizumab during maintenance treatment phase until loss of clinical benefit.	
Reporting group title	Arm B (Nab-Paclitaxel+Carboplatin)
Reporting group description:	
Subjects will receive IV infusion of carboplatin on Day 1 and nab-paclitaxel on Days 1, 8, and 15 of each 21-day cycle for 4 or 6 cycles or until disease progression whichever occurs first during induction treatment phase. Subjects will receive best supportive care during maintenance treatment phase. Switch maintenance to pemetrexed is also permitted. Subjects who were consented prior to approval of protocol Version 5 will be given the option to cross over to receive atezolizumab as monotherapy until disease progression.	

Reporting group values	Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin)	Arm B (Nab-Paclitaxel+Carboplatin)	Total
Number of subjects	483	240	723
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)	245	117	362
From 65-84 years	236	122	358
85 years and over	2	1	3
Age continuous Units: years			
arithmetic mean	63.8	64.4	
standard deviation	± 9.5	± 8.9	-
Gender categorical Units: Subjects			
Female	206	102	308
Male	277	138	415

End points

End points reporting groups

Reporting group title	Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin)

Reporting group description:

Subjects will receive intravenous (IV) infusion of atezolizumab and carboplatin on Day 1 of each 21-day cycle, and nab-paclitaxel on Days 1, 8, and 15 of each 21-day cycle for 4 or 6 cycles or until loss of clinical benefit whichever occurs first during induction treatment phase. Subjects will receive IV infusion of atezolizumab during maintenance treatment phase until loss of clinical benefit.

Reporting group title	Arm B (Nab-Paclitaxel+Carboplatin)

Reporting group description:

Subjects will receive IV infusion of carboplatin on Day 1 and nab-paclitaxel on Days 1, 8, and 15 of each 21-day cycle for 4 or 6 cycles or until disease progression whichever occurs first during induction treatment phase. Subjects will receive best supportive care during maintenance treatment phase. Switch maintenance to pemetrexed is also permitted. Subjects who were consented prior to approval of protocol Version 5 will be given the option to cross over to receive atezolizumab as monotherapy until disease progression.

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 ITT-WT 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 ITT-WT Population

End point description:

PFS is reported for the ITT-WT population. The term "wild type" (WT) refers to randomized subjects who do not have a sensitizing EGFR mutation or ALK translocation.

End point type	Primary

End point timeframe:

Up to approximately 35 months after first patient enrolled

End point values	Arm A (Atezolizumab +Nab-Paclitaxel+Carboplatin)	Arm B (Nab-Paclitaxel+Carboplatin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	451	228		
Units: Months				
median (confidence interval 95%)				
PFS in the ITT-WT Population	7.0 (6.2 to 7.3)	5.5 (4.4 to 5.9)		

Statistical analyses

Statistical analysis title	Statistical Analysis for PFS in the ITT-WT
Comparison groups	Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin) v Arm B (Nab-Paclitaxel+Carboplatin)

Number of subjects included in analysis	679
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Stratified Log Rank Test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	0.77

Primary: Overall Survival (OS) in the ITT-WT Population

End point title	Overall Survival (OS) in the ITT-WT Population

End point description:

OS is reported for the ITT-WT population. The term "wild type" (WT) refers to randomized subjects who do not have a sensitizing EGFR mutation or ALK translocation.

End point type	Primary

End point timeframe:

Up to approximately 35 months after first patient enrolled

End point values	Arm A (Atezolizumab +Nab-Paclitaxel+Carboplatin)	Arm B (Nab-Paclitaxel+Carboplatin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	451	228		
Units: Months				
median (confidence interval 95%)	18.6 (16.0 to 21.2)	13.9 (12.0 to 18.7)		

Statistical analyses

Statistical analysis title	Statistical Analysis for OS in the ITT-WT
Comparison groups	Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin) v Arm B (Nab-Paclitaxel+Carboplatin)
Number of subjects included in analysis	679
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0331
Method	Startified Log-Rank Test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.79

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	0.98

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

End point title	PFS 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 56 months after first subject enrolled

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

Statistical analyses

No statistical analyses for this end point

Secondary: OS as Determined by the Investigator Using Recist v1.1 in the ITT Population

End point title	OS 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 56 months after first subject enrolled

End point values	Arm A (Atezolizumab +Nab-Paclitaxel+Carboplatin)	Arm B (Nab-Paclitaxel+Carboplatin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[3]	0[4]		
Units: Months				
median (standard deviation)	()	()		

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With an Objective Response (OR) (Complete Response [CR] or Partial Response [PR]) as Determined by the Investigator Using RECIST v1.1 in the ITT-WT Population

End point title	Percentage of Participants With an Objective Response (OR) (Complete Response [CR] or Partial Response [PR]) as Determined by the Investigator Using RECIST v1.1 in the ITT-WT Population

End point description:

End point type	Secondary

End point timeframe:

Up to approximately 56 months after first subject enrolled

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

Notes:

[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: Duration of Response (DOR) as Determined by the Investigator Using RECIST v1.1 in ITT-WT Population

End point title	Duration of Response (DOR) as Determined by the Investigator Using RECIST v1.1 in ITT-WT Population

End point description:

End point type	Secondary

End point timeframe:

Up to approximately 56 months after first subject enrolled

End point values	Arm A (Atezolizumab +Nab-Paclitaxel+Carboplatin)	Arm B (Nab-Paclitaxel+Carboplatin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[7]	0[8]		
Units: Months				
median (standard deviation)	()	()		

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who are Alive at Year 1 and 2 in ITT-WT Population

End point title	Percentage of Subjects Who are Alive at Year 1 and 2 in ITT-WT Population

End point description:

Percentage of subjects who are alive is reported for the ITT-WT population. The term "wild type" (WT) refers to randomized subjects who do not have a sensitizing EGFR mutation or ALK translocation.

End point type	Secondary

End point timeframe:

Up to approximately 56 months after first subject enrolled

End point values	Arm A (Atezolizumab +Nab-Paclitaxel+Carboplatin)	Arm B (Nab-Paclitaxel+Carboplatin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[9]	0[10]		
Units: Percentage				
number (not applicable)				

Notes:

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

[10] - 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 in the ITT-WT Population

End point title	Time to Deterioration (TTD) in Patient-Reported Lung Cancer Symptoms in the ITT-WT Population

End point description:

Defined as time from randomization to confirmed deterioration (10-point change) on the combined European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire−Core (EORTC QLQ-C30) and supplemental lung cancer module (EORTC QLQ-LC13) symptom subscales.

End point type	Secondary

End point timeframe:

Up to approximately 56 months after first subject enrolled

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

Notes:

[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: Change From Baseline in Patient-Reported Lung Cancer Symptoms Score Using the Symptoms in Lung Cancer (SILC) Scale

End point title	Change From Baseline in Patient-Reported Lung Cancer Symptoms Score Using the Symptoms in Lung Cancer (SILC) Scale

End point description:

End point type	Secondary

End point timeframe:

Up to approximately 56 months after first subject enrolled date

End point values	Arm A (Atezolizumab +Nab-Paclitaxel+Carboplatin)	Arm B (Nab-Paclitaxel+Carboplatin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[13]	0[14]		
Units: Units on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:
[13] - Data will be analyzed at the time of study completion.
[14] - 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 56 months after first subject enrolled date

End point values	Arm A (Atezolizumab +Nab-Paclitaxel+Carboplatin)	Arm B (Nab-Paclitaxel+Carboplatin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[15]	0[16]		
Units: Percentage				
number (not applicable)				

Notes:
[15] - Data will be analyzed at the time of study completion.
[16] - 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 Antibodies (ATAs) to Atezolizumab

End point title	Percentage of Participants With Anti-Therapeutic Antibodies (ATAs) to Atezolizumab

End point description:

End point type	Secondary

End point timeframe:
Up to approximately 56 months after first subject enrolled

End point values	Arm A (Atezolizumab +Nab-Paclitaxel+Carboplatin)	Arm B (Nab-Paclitaxel+Carboplatin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[17]	0[18]		
Units: Percentage				
number (not applicable)				

Notes:

[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: Maximum Observed Serum Concentration (Cmax) of Atezolizumab in Atezolizumab+Carboplatin+Nab-Paclitaxel Arm

End point title	Maximum Observed Serum Concentration (Cmax) of Atezolizumab in Atezolizumab+Carboplatin+Nab-Paclitaxel Arm[19]

End point description:

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 (D) 1 of Cycle (Cy) 1,2,3,4,8,16 and every 8 cycles thereafter up to end of treatment (EOT) (approximately 56 months), 0.5 hours (h) post-infusion on D1 of Cy1,3, at 120 days after EOT (up to approximately 56 months)

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Cmax of Atezolizumab is only relevant for arm with Atezolizumab.

End point values	Arm A (Atezolizumab +Nab-Paclitaxel+Carboplatin)			
Subject group type	Reporting group			
Number of subjects analysed	0[20]			
Units: mcg/mL				
geometric mean (standard deviation)	()			

Notes:

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

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Observed Serum Concentration (Cmin) of Atezolizumab Prior to Infusion in Atezolizumab+Carboplatin+Nab-Paclitaxel Arm

End point title	Minimum Observed Serum Concentration (Cmin) of Atezolizumab Prior to Infusion in Atezolizumab+Carboplatin+Nab-Paclitaxel Arm[21]

End point description:

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

End point type	Secondary

End point timeframe:

Predose on D1 of Cy 1, 2, 3, 4, 8, 16 and every 8 cycles thereafter up to EOT (up to approximately 56 months), at 120 days after EOT (up to approximately 56 months)]

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Cmin of Atezolizumab is only relevant for arm with Atezolizumab.

End point values	Arm A (Atezolizumab +Nab-Paclitaxel+Carboplatin)			
Subject group type	Reporting group			
Number of subjects analysed	0[22]			
Units: mcg/mL				
geometric mean (standard deviation)	()			

Notes:

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

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of Carboplatin

End point title	Plasma Concentration of Carboplatin

End point description:

End point type	Secondary

End point timeframe:

Predose (same day of treatment administration), 5-10 minutes before end of carboplatin infusion, 1 h after carboplatin infusion (infusion duration=15 to 30 minutes) on D1 of Cy1,3 (1Cy=21 days)(up to approximately 56 months)

End point values	Arm A (Atezolizumab +Nab-Paclitaxel+Carboplatin)	Arm B (Nab-Paclitaxel+Carboplatin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[23]	0[24]		
Units: mcg/mL				
geometric mean (standard deviation)	()	()		

Notes:

[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: Plasma Concentrations of Nab-Paclitaxel Reported as Total Paclitaxel

End point title	Plasma Concentrations of Nab-Paclitaxel Reported as Total Paclitaxel

End point description:

End point type	Secondary

End point timeframe:

Predose (same day of treatment administration), 5-10 minutes before end of nab-paclitaxel infusion, 1 h after nab-paclitaxel infusion (infusion duration=30 minutes) on D1 of Cy1,3 (1Cy=21 days)(up to approximately 56 months)

End point values	Arm A (Atezolizumab +Nab-Paclitaxel+Carboplatin)	Arm B (Nab-Paclitaxel+Carboplatin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[25]	0[26]		
Units: mcg/mL				
geometric mean (standard deviation)	()	()		

Notes:

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

[26] - 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: 15 March 2018	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups	
Reporting group title	Arm B (Nab-Paclitaxel+Carboplatin)
Reporting group description:	
Subjects will receive IV infusion of carboplatin on Day 1 and nab-paclitaxel on Days 1, 8, and 15 of each 21-day cycle for 4 or 6 cycles or until disease progression whichever occurs first during induction treatment phase. Subjects will receive best supportive care during maintenance treatment phase. Switch maintenance to pemetrexed is also permitted. Subjects who were consented prior to approval of protocol Version 5 will be given the option to cross over to receive atezolizumab as monotherapy until disease progression.	
Reporting group title	Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin)
Reporting group description:	
Subjects will receive intravenous (IV) infusion of atezolizumab and carboplatin on Day 1 of each 21-day cycle, and nab-paclitaxel on Days 1, 8, and 15 of each 21-day cycle for 4 or 6 cycles or until loss of clinical benefit whichever occurs first during induction treatment phase. Subjects will receive IV infusion of atezolizumab during maintenance treatment phase until loss of clinical benefit.	

Serious adverse events	Arm B (Nab-Paclitaxel+Carboplatin)	Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin)	
Total subjects affected by serious adverse events			
subjects affected / exposed	88 / 232 (37.93%)	240 / 473 (50.74%)	
number of deaths (all causes)	134	240	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
TUMOUR PAIN			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
ARTERIAL OCCLUSIVE DISEASE			
subjects affected / exposed	2 / 232 (0.86%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEEP VEIN THROMBOSIS			

subjects affected / exposed	0 / 232 (0.00%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
EMBOLISM			
subjects affected / exposed	1 / 232 (0.43%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMORAL ARTERY ANEURYSM			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOTENSION			
subjects affected / exposed	1 / 232 (0.43%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
JUGULAR VEIN THROMBOSIS			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PHLEBITIS			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VASCULAR STENOSIS			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
ABORTION INDUCED			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

ASTHENIA			
subjects affected / exposed	0 / 232 (0.00%)	3 / 473 (0.63%)	
occurrences causally related to treatment / all	0 / 0	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHEST PAIN			
subjects affected / exposed	0 / 232 (0.00%)	5 / 473 (1.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEATH			
subjects affected / exposed	4 / 232 (1.72%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 4	1 / 1	
deaths causally related to treatment / all	0 / 4	1 / 1	
DRUG INTERACTION			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FATIGUE			
subjects affected / exposed	2 / 232 (0.86%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	2 / 232 (0.86%)	4 / 473 (0.85%)	
occurrences causally related to treatment / all	2 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
GENERALISED OEDEMA			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	0 / 232 (0.00%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUCOSAL INFLAMMATION			

subjects affected / exposed	0 / 232 (0.00%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
NON−CARDIAC CHEST PAIN			
subjects affected / exposed	0 / 232 (0.00%)	3 / 473 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
OEDEMA PERIPHERAL			
subjects affected / exposed	1 / 232 (0.43%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PAIN			
subjects affected / exposed	0 / 232 (0.00%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERFORMANCE STATUS DECREASED			
subjects affected / exposed	0 / 232 (0.00%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYREXIA			
subjects affected / exposed	2 / 232 (0.86%)	8 / 473 (1.69%)	
occurrences causally related to treatment / all	1 / 2	6 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUDDEN DEATH			
subjects affected / exposed	1 / 232 (0.43%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Immune system disorders			
ANAPHYLACTIC REACTION			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			

VAGINAL HAEMORRHAGE			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
ACUTE RESPIRATORY FAILURE			
subjects affected / exposed	0 / 232 (0.00%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASPIRATION			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
ASTHMA			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHRONIC OBSTRUCTIVE PULMONARY DISEASE			
subjects affected / exposed	3 / 232 (1.29%)	12 / 473 (2.54%)	
occurrences causally related to treatment / all	1 / 4	0 / 17	
deaths causally related to treatment / all	0 / 1	0 / 0	
COUGH			
subjects affected / exposed	1 / 232 (0.43%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPNOEA			
subjects affected / exposed	1 / 232 (0.43%)	11 / 473 (2.33%)	
occurrences causally related to treatment / all	0 / 1	1 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
EPISTAXIS			
subjects affected / exposed	1 / 232 (0.43%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

HAEMOPTYSIS			
subjects affected / exposed	3 / 232 (1.29%)	5 / 473 (1.06%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG DISORDER			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ORGANISING PNEUMONIA			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OROPHARYNGEAL DISCOMFORT			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLEURAL EFFUSION			
subjects affected / exposed	0 / 232 (0.00%)	8 / 473 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONITIS			
subjects affected / exposed	3 / 232 (1.29%)	7 / 473 (1.48%)	
occurrences causally related to treatment / all	1 / 3	7 / 7	
deaths causally related to treatment / all	0 / 1	2 / 2	
PNEUMOTHORAX			
subjects affected / exposed	2 / 232 (0.86%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOTHORAX SPONTANEOUS			
subjects affected / exposed	0 / 232 (0.00%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY EMBOLISM			

subjects affected / exposed	5 / 232 (2.16%)	14 / 473 (2.96%)	
occurrences causally related to treatment / all	1 / 5	0 / 15	
deaths causally related to treatment / all	0 / 1	0 / 4	
PULMONARY HAEMORRHAGE			
subjects affected / exposed	0 / 232 (0.00%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY DISTRESS			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
RESPIRATORY FAILURE			
subjects affected / exposed	2 / 232 (0.86%)	3 / 473 (0.63%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
CONFUSIONAL STATE			
subjects affected / exposed	0 / 232 (0.00%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DISORIENTATION			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MENTAL STATUS CHANGES			
subjects affected / exposed	0 / 232 (0.00%)	4 / 473 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 232 (0.00%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	0 / 232 (0.00%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
BLOOD CREATININE INCREASED			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BLOOD GLUCOSE INCREASED			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LYMPHOCYTE COUNT DECREASED			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	0 / 232 (0.00%)	6 / 473 (1.27%)	
occurrences causally related to treatment / all	0 / 0	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLATELET COUNT DECREASED			
subjects affected / exposed	1 / 232 (0.43%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	0 / 232 (0.00%)	4 / 473 (0.85%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	1 / 232 (0.43%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMORAL NECK FRACTURE			
subjects affected / exposed	1 / 232 (0.43%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMUR FRACTURE			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFUSION RELATED REACTION			
subjects affected / exposed	0 / 232 (0.00%)	3 / 473 (0.63%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
PUBIS FRACTURE			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPINAL COMPRESSION FRACTURE			
subjects affected / exposed	1 / 232 (0.43%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPINAL FRACTURE			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER LIMB FRACTURE			
subjects affected / exposed	1 / 232 (0.43%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	1 / 232 (0.43%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANGINA UNSTABLE			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL FIBRILLATION			
subjects affected / exposed	1 / 232 (0.43%)	3 / 473 (0.63%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL FLUTTER			
subjects affected / exposed	0 / 232 (0.00%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRADYCARDIA			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC ANEURYSM			
subjects affected / exposed	1 / 232 (0.43%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC ARREST			
subjects affected / exposed	0 / 232 (0.00%)	3 / 473 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 2	
CARDIAC FAILURE			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC FAILURE CHRONIC			

subjects affected / exposed	1 / 232 (0.43%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC TAMPONADE			
subjects affected / exposed	0 / 232 (0.00%)	3 / 473 (0.63%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIO−RESPIRATORY ARREST			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
MYOCARDIAL INFARCTION			
subjects affected / exposed	1 / 232 (0.43%)	3 / 473 (0.63%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 3	
PALPITATIONS			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERICARDIAL EFFUSION			
subjects affected / exposed	0 / 232 (0.00%)	6 / 473 (1.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUPRAVENTRICULAR TACHYCARDIA			
subjects affected / exposed	0 / 232 (0.00%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
VENTRICULAR TACHYCARDIA			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Nervous system disorders			
ATAXIA			

subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CAROTID ARTERY STENOSIS			
subjects affected / exposed	1 / 232 (0.43%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	2 / 232 (0.86%)	3 / 473 (0.63%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIZZINESS			
subjects affected / exposed	0 / 232 (0.00%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
EMBOLIC STROKE			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
EPILEPSY			
subjects affected / exposed	1 / 232 (0.43%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEADACHE			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEMIPARESIS			
subjects affected / exposed	1 / 232 (0.43%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ISCHAEMIC STROKE			

subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LETHARGY			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PARAESTHESIA			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEIZURE			
subjects affected / exposed	0 / 232 (0.00%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
TOXIC NEUROPATHY			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYNCOPE			
subjects affected / exposed	1 / 232 (0.43%)	3 / 473 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
VASOGENIC CEREBRAL OEDEMA			
subjects affected / exposed	1 / 232 (0.43%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
AGRANULOCYTOSIS			
subjects affected / exposed	1 / 232 (0.43%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANAEMIA			

subjects affected / exposed	8 / 232 (3.45%)	13 / 473 (2.75%)	
occurrences causally related to treatment / all	6 / 8	12 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEBRILE NEUTROPENIA			
subjects affected / exposed	5 / 232 (2.16%)	9 / 473 (1.90%)	
occurrences causally related to treatment / all	5 / 5	10 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMOLYTIC URAEMIC SYNDROME			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LEUKOPENIA			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIA			
subjects affected / exposed	2 / 232 (0.86%)	14 / 473 (2.96%)	
occurrences causally related to treatment / all	2 / 2	16 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCYTOPENIA			
subjects affected / exposed	1 / 232 (0.43%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOCYTOPENIA			
subjects affected / exposed	0 / 232 (0.00%)	6 / 473 (1.27%)	
occurrences causally related to treatment / all	0 / 0	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

ABDOMINAL PAIN			
subjects affected / exposed	1 / 232 (0.43%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL PAIN LOWER			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
AUTOIMMUNE COLITIS			
subjects affected / exposed	0 / 232 (0.00%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
COLITIS			
subjects affected / exposed	0 / 232 (0.00%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONSTIPATION			
subjects affected / exposed	1 / 232 (0.43%)	3 / 473 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	2 / 232 (0.86%)	14 / 473 (2.96%)	
occurrences causally related to treatment / all	1 / 2	12 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
DUODENAL ULCER			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRITIS			

subjects affected / exposed	1 / 232 (0.43%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 232 (0.00%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL VASCULAR MALFORMATION HAEMORRHAGIC			
subjects affected / exposed	1 / 232 (0.43%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ILEUS PARALYTIC			
subjects affected / exposed	1 / 232 (0.43%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LARGE INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LARGE INTESTINAL STENOSIS			
subjects affected / exposed	1 / 232 (0.43%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MELAENA			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NAUSEA			

subjects affected / exposed	4 / 232 (1.72%)	5 / 473 (1.06%)	
occurrences causally related to treatment / all	3 / 5	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
OESOPHAGEAL FOOD IMPACTION			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	2 / 232 (0.86%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
STOMATITIS			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			
subjects affected / exposed	4 / 232 (1.72%)	6 / 473 (1.27%)	
occurrences causally related to treatment / all	3 / 5	4 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
AUTOIMMUNE HEPATITIS			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BILE DUCT STONE			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLECYSTITIS ACUTE			

subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLESTASIS			
subjects affected / exposed	1 / 232 (0.43%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC CIRRHOSIS			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
HEPATITIS			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATOCELLULAR INJURY			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
IMMUNE−MEDIATED HEPATITIS			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
DRUG ERUPTION			
subjects affected / exposed	1 / 232 (0.43%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RASH			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SKIN ULCER			

subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	0 / 232 (0.00%)	4 / 473 (0.85%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEPHRITIS			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEPHROLITHIASIS			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEPHROPATHY TOXIC			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
POSTRENAL FAILURE			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL FAILURE			
subjects affected / exposed	2 / 232 (0.86%)	5 / 473 (1.06%)	
occurrences causally related to treatment / all	1 / 2	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
TUBULOINTERSTITIAL NEPHRITIS			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			

ADRENAL INSUFFICIENCY			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOTHYROIDISM			
subjects affected / exposed	0 / 232 (0.00%)	3 / 473 (0.63%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	0 / 232 (0.00%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
BACK PAIN			
subjects affected / exposed	0 / 232 (0.00%)	3 / 473 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
BONE PAIN			
subjects affected / exposed	0 / 232 (0.00%)	3 / 473 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCULAR WEAKNESS			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	0 / 232 (0.00%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYALGIA			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

SPINAL PAIN			
subjects affected / exposed	1 / 232 (0.43%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
APPENDICITIS PERFORATED			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATYPICAL PNEUMONIA			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BACTERAEMIA			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BACTERIAL COLITIS			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BACTERIAL SEPSIS			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHITIS			
subjects affected / exposed	1 / 232 (0.43%)	5 / 473 (1.06%)	
occurrences causally related to treatment / all	0 / 1	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
CAMPYLOBACTER INFECTION			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CATHETER SITE INFECTION			

subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CELLULITIS			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CLOSTRIDIUM DIFFICILE INFECTION			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONJUNCTIVITIS			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CYSTITIS			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEVICE RELATED INFECTION			
subjects affected / exposed	1 / 232 (0.43%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIVERTICULITIS			
subjects affected / exposed	1 / 232 (0.43%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENCEPHALITIS			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ERYSIPELAS			

subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEBRILE INFECTION			
subjects affected / exposed	0 / 232 (0.00%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
GANGRENE			
subjects affected / exposed	1 / 232 (0.43%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTION			
subjects affected / exposed	1 / 232 (0.43%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTIOUS PLEURAL EFFUSION			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFLUENZA			
subjects affected / exposed	1 / 232 (0.43%)	5 / 473 (1.06%)	
occurrences causally related to treatment / all	0 / 1	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG INFECTION			
subjects affected / exposed	1 / 232 (0.43%)	14 / 473 (2.96%)	
occurrences causally related to treatment / all	0 / 1	5 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
NASOPHARYNGITIS			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIC INFECTION			

subjects affected / exposed	1 / 232 (0.43%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	14 / 232 (6.03%)	28 / 473 (5.92%)	
occurrences causally related to treatment / all	3 / 16	6 / 36	
deaths causally related to treatment / all	0 / 2	0 / 5	
PULMONARY SEPSIS			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 232 (0.43%)	3 / 473 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPSIS			
subjects affected / exposed	2 / 232 (0.86%)	6 / 473 (1.27%)	
occurrences causally related to treatment / all	1 / 2	1 / 6	
deaths causally related to treatment / all	1 / 2	0 / 1	
SEPTIC SHOCK			
subjects affected / exposed	2 / 232 (0.86%)	5 / 473 (1.06%)	
occurrences causally related to treatment / all	0 / 2	3 / 5	
deaths causally related to treatment / all	0 / 1	1 / 1	
STAPHYLOCOCCAL SEPSIS			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
TRACHEOBRONCHITIS			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER RESPIRATORY TRACT INFECTION			

subjects affected / exposed	0 / 232 (0.00%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 232 (0.43%)	4 / 473 (0.85%)	
occurrences causally related to treatment / all	1 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
UROSEPSIS			
subjects affected / exposed	1 / 232 (0.43%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	2 / 232 (0.86%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEHYDRATION			
subjects affected / exposed	2 / 232 (0.86%)	3 / 473 (0.63%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIABETES MELLITUS			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIABETIC KETOACIDOSIS			
subjects affected / exposed	1 / 232 (0.43%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERGLYCAEMIA			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERKALAEMIA			

subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOALBUMINAEMIA			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOCALCAEMIA			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOKALAEMIA			
subjects affected / exposed	2 / 232 (0.86%)	3 / 473 (0.63%)	
occurrences causally related to treatment / all	1 / 2	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOMAGNESAEMIA			
subjects affected / exposed	0 / 232 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPONATRAEMIA			
subjects affected / exposed	0 / 232 (0.00%)	3 / 473 (0.63%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
TYPE 2 DIABETES MELLITUS			
subjects affected / exposed	1 / 232 (0.43%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm B (Nab-Paclitaxel+Carboplatin)	Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	226 / 232 (97.41%)	466 / 473 (98.52%)	
Vascular disorders			
HYPOTENSION			
subjects affected / exposed	13 / 232 (5.60%)	32 / 473 (6.77%)	
occurrences (all)	14	40	
HYPERTENSION			
subjects affected / exposed	8 / 232 (3.45%)	24 / 473 (5.07%)	
occurrences (all)	10	29	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	38 / 232 (16.38%)	84 / 473 (17.76%)	
occurrences (all)	53	121	
CHEST PAIN			
subjects affected / exposed	12 / 232 (5.17%)	26 / 473 (5.50%)	
occurrences (all)	12	31	
FATIGUE			
subjects affected / exposed	109 / 232 (46.98%)	222 / 473 (46.93%)	
occurrences (all)	133	276	
OEDEMA PERIPHERAL			
subjects affected / exposed	25 / 232 (10.78%)	64 / 473 (13.53%)	
occurrences (all)	28	71	
PAIN			
subjects affected / exposed	7 / 232 (3.02%)	26 / 473 (5.50%)	
occurrences (all)	8	30	
PYREXIA			
subjects affected / exposed	21 / 232 (9.05%)	75 / 473 (15.86%)	
occurrences (all)	29	96	
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	38 / 232 (16.38%)	125 / 473 (26.43%)	
occurrences (all)	41	145	
DYSPNOEA			

subjects affected / exposed	46 / 232 (19.83%)	126 / 473 (26.64%)	
occurrences (all)	54	158	
EPISTAXIS			
subjects affected / exposed	27 / 232 (11.64%)	68 / 473 (14.38%)	
occurrences (all)	30	83	
HAEMOPTYSIS			
subjects affected / exposed	7 / 232 (3.02%)	26 / 473 (5.50%)	
occurrences (all)	7	33	
PRODUCTIVE COUGH			
subjects affected / exposed	8 / 232 (3.45%)	33 / 473 (6.98%)	
occurrences (all)	8	37	
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	8 / 232 (3.45%)	28 / 473 (5.92%)	
occurrences (all)	8	28	
DEPRESSION			
subjects affected / exposed	5 / 232 (2.16%)	25 / 473 (5.29%)	
occurrences (all)	5	25	
INSOMNIA			
subjects affected / exposed	31 / 232 (13.36%)	68 / 473 (14.38%)	
occurrences (all)	33	74	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	14 / 232 (6.03%)	24 / 473 (5.07%)	
occurrences (all)	18	34	
BLOOD CREATININE INCREASED			
subjects affected / exposed	7 / 232 (3.02%)	25 / 473 (5.29%)	
occurrences (all)	12	29	
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	35 / 232 (15.09%)	93 / 473 (19.66%)	
occurrences (all)	61	187	
PLATELET COUNT DECREASED			
subjects affected / exposed	38 / 232 (16.38%)	107 / 473 (22.62%)	
occurrences (all)	61	177	
WEIGHT DECREASED			

subjects affected / exposed	28 / 232 (12.07%)	53 / 473 (11.21%)	
occurrences (all)	29	58	
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	18 / 232 (7.76%)	49 / 473 (10.36%)	
occurrences (all)	28	80	
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	25 / 232 (10.78%)	74 / 473 (15.64%)	
occurrences (all)	36	85	
DYSGEUSIA			
subjects affected / exposed	14 / 232 (6.03%)	57 / 473 (12.05%)	
occurrences (all)	14	60	
HEADACHE			
subjects affected / exposed	23 / 232 (9.91%)	77 / 473 (16.28%)	
occurrences (all)	26	92	
NEUROPATHY PERIPHERAL			
subjects affected / exposed	21 / 232 (9.05%)	53 / 473 (11.21%)	
occurrences (all)	25	55	
PARAESTHESIA			
subjects affected / exposed	12 / 232 (5.17%)	40 / 473 (8.46%)	
occurrences (all)	13	48	
PERIPHERAL SENSORY NEUROPATHY			
subjects affected / exposed	23 / 232 (9.91%)	60 / 473 (12.68%)	
occurrences (all)	29	69	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	116 / 232 (50.00%)	255 / 473 (53.91%)	
occurrences (all)	132	346	
LEUKOPENIA			
subjects affected / exposed	18 / 232 (7.76%)	51 / 473 (10.78%)	
occurrences (all)	28	91	
NEUTROPENIA			
subjects affected / exposed	105 / 232 (45.26%)	212 / 473 (44.82%)	
occurrences (all)	194	422	
THROMBOCYTOPENIA			

subjects affected / exposed	60 / 232 (25.86%)	130 / 473 (27.48%)	
occurrences (all)	95	206	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	17 / 232 (7.33%)	51 / 473 (10.78%)	
occurrences (all)	20	62	
CONSTIPATION			
subjects affected / exposed	71 / 232 (30.60%)	168 / 473 (35.52%)	
occurrences (all)	89	213	
DIARRHOEA			
subjects affected / exposed	71 / 232 (30.60%)	193 / 473 (40.80%)	
occurrences (all)	100	300	
DYSPEPSIA			
subjects affected / exposed	7 / 232 (3.02%)	30 / 473 (6.34%)	
occurrences (all)	8	31	
NAUSEA			
subjects affected / exposed	106 / 232 (45.69%)	231 / 473 (48.84%)	
occurrences (all)	148	345	
STOMATITIS			
subjects affected / exposed	12 / 232 (5.17%)	37 / 473 (7.82%)	
occurrences (all)	14	41	
VOMITING			
subjects affected / exposed	43 / 232 (18.53%)	125 / 473 (26.43%)	
occurrences (all)	67	214	
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	63 / 232 (27.16%)	151 / 473 (31.92%)	
occurrences (all)	63	153	
DRY SKIN			
subjects affected / exposed	12 / 232 (5.17%)	24 / 473 (5.07%)	
occurrences (all)	12	27	
PRURITUS			
subjects affected / exposed	12 / 232 (5.17%)	53 / 473 (11.21%)	
occurrences (all)	12	63	
RASH			

subjects affected / exposed	16 / 232 (6.90%)	66 / 473 (13.95%)	
occurrences (all)	18	77	
Endocrine disorders			
HYPOTHYROIDISM			
subjects affected / exposed	1 / 232 (0.43%)	50 / 473 (10.57%)	
occurrences (all)	1	54	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	24 / 232 (10.34%)	70 / 473 (14.80%)	
occurrences (all)	26	89	
BACK PAIN			
subjects affected / exposed	16 / 232 (6.90%)	79 / 473 (16.70%)	
occurrences (all)	16	87	
MUSCULAR WEAKNESS			
subjects affected / exposed	14 / 232 (6.03%)	22 / 473 (4.65%)	
occurrences (all)	16	24	
MUSCULOSKELETAL PAIN			
subjects affected / exposed	10 / 232 (4.31%)	45 / 473 (9.51%)	
occurrences (all)	10	53	
MYALGIA			
subjects affected / exposed	10 / 232 (4.31%)	41 / 473 (8.67%)	
occurrences (all)	11	48	
PAIN IN EXTREMITY			
subjects affected / exposed	14 / 232 (6.03%)	52 / 473 (10.99%)	
occurrences (all)	14	58	
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	6 / 232 (2.59%)	26 / 473 (5.50%)	
occurrences (all)	7	27	
NASOPHARYNGITIS			
subjects affected / exposed	9 / 232 (3.88%)	29 / 473 (6.13%)	
occurrences (all)	9	39	
PNEUMONIA			
subjects affected / exposed	5 / 232 (2.16%)	27 / 473 (5.71%)	
occurrences (all)	5	28	
UPPER RESPIRATORY TRACT INFECTION			

subjects affected / exposed	12 / 232 (5.17%)	33 / 473 (6.98%)	
occurrences (all)	15	47	
URINARY TRACT INFECTION			
subjects affected / exposed	19 / 232 (8.19%)	59 / 473 (12.47%)	
occurrences (all)	20	79	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	58 / 232 (25.00%)	142 / 473 (30.02%)	
occurrences (all)	64	164	
DEHYDRATION			
subjects affected / exposed	24 / 232 (10.34%)	47 / 473 (9.94%)	
occurrences (all)	30	68	
HYPOKALAEMIA			
subjects affected / exposed	24 / 232 (10.34%)	71 / 473 (15.01%)	
occurrences (all)	29	90	
HYPOMAGNESAEMIA			
subjects affected / exposed	39 / 232 (16.81%)	94 / 473 (19.87%)	
occurrences (all)	48	125	
HYPONATRAEMIA			
subjects affected / exposed	8 / 232 (3.45%)	26 / 473 (5.50%)	
occurrences (all)	10	41	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 August 2015	Protocol was amended to include change to the name of the test product from MPDL3280A to atezolizumab. The evaluations of progression-free survival at 6 months and at 1 year and overall survival at 3 years have been added as exploratory objectives to further evaluate the clinical benefit of atezolizumab at these time points. The contraception requirements in the inclusion and exclusion criteria and the pregnancy-reporting information have been updated to be consistent with safety information for nab-paclitaxel. The study inclusion criteria have been modified, on the basis of data from 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 data from 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 criterion 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 because this is in conflict with Section 4.5.5. Patients with contraindications to contrast may have assessments done with non-contrast computed tomography or MRI.
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. For patients consented and randomized to Arm B after Ethics Committee or Institutional Review Board approval of Protocol GO29537, Version 5 at each respective site, the option for crossover to atezolizumab maintenance therapy has been removed to enable the comparative analyses of the two treatment arms. Patients randomized to Arm B who were consented under previous versions of this protocol prior to the approval of Version 5 will continue to have the option for crossover to atezolizumab maintenance therapy. The total number of patients to be randomized in the study has increased from 550 patients to 650 patients to ensure that the study is adequately powered for the comparative analyses. Erlotinib switch maintenance therapy has been removed from the protocol. A secondary efficacy objective and outcome measure has been 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 intent-to-treat (ITT) and programmed death−ligand 1(PD-L1)−selected populations.

01 March 2017	Protocol was amended to include change to the primary analysis populations for 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 and a 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. Patients with known sensitizing EGFR mutations or ALK translocations will be excluded from the primary analysis populations. The analyses of PFS and OS in all randomized patients will be conducted as secondary analyses. Additional censoring rule for the primary endpoint of PFS for U.S. registration purposes has been removed. The statistical testing procedures have been amended to reflect the change in analysis populations. All endpoints (secondary and exploratory) based on the review by an Independent Review Facility (IRF) have been removed.
24 October 2018	Protocol was amended to correct the end of study definition corrected. This correction ensures that the study continues until last patient, last visit or until the Sponsor terminates the study. The inclusion criterion that addresses female contraception has been modified to specify when women must refrain from donating eggs.
29 March 2019	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 initiation of a new anticancer therapy, whichever occurs first.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported