Clinical trial results:
A Phase III, Multicenter, Randomized, Placebo-Controlled Study of Atezolizumab (Anti-PD-L1 Antibody) as Monotherapy and in Combination With Platinum-Based Chemotherapy in Patients With Untreated Locally Advanced or Metastatic Urothelial Carcinoma

Summary

EudraCT number	2016-000250-35
Trial protocol	ES CZ EE GR PL SI GB FI NL PT BE IT
Global end of trial date	

Results information

Result version number	v1
This version publication date	08 September 2023
First version publication date	08 September 2023

Trial information

Trial identification

Sponsor protocol code	WO30070

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02807636
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, 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	31 August 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2022
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

This study evaluated the efficacy of atezolizumab given as monotherapy or in combination with platinum-based chemotherapy versus placebo in combination with platinum-based chemotherapy in participants with locally advanced or metastatic urothelial carcinoma who have not received prior systemic therapy.

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	30 June 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	39 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 30
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Bosnia and Herzegovina: 12
Country: Number of subjects enrolled	Brazil: 61
Country: Number of subjects enrolled	Canada: 21
Country: Number of subjects enrolled	Chile: 13
Country: Number of subjects enrolled	China: 40
Country: Number of subjects enrolled	Czechia: 27
Country: Number of subjects enrolled	Spain: 204
Country: Number of subjects enrolled	Estonia: 7
Country: Number of subjects enrolled	Finland: 5
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Georgia: 18
Country: Number of subjects enrolled	Greece: 47
Country: Number of subjects enrolled	Hong Kong: 17
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Italy: 94
Country: Number of subjects enrolled	Japan: 58
Country: Number of subjects enrolled	Korea, Republic of: 72
Country: Number of subjects enrolled	Mexico: 14

Country: Number of subjects enrolled	Malaysia: 5
Country: Number of subjects enrolled	Netherlands: 12
Country: Number of subjects enrolled	Poland: 33
Country: Number of subjects enrolled	Portugal: 7
Country: Number of subjects enrolled	Romania: 9
Country: Number of subjects enrolled	Russian Federation: 68
Country: Number of subjects enrolled	Singapore: 8
Country: Number of subjects enrolled	Serbia: 22
Country: Number of subjects enrolled	Slovenia: 17
Country: Number of subjects enrolled	Thailand: 23
Country: Number of subjects enrolled	Turkey: 91
Country: Number of subjects enrolled	Taiwan: 42
Country: Number of subjects enrolled	Ukraine: 27
Country: Number of subjects enrolled	United States: 77
Country: Number of subjects enrolled	South Africa: 13
Worldwide total number of subjects	1213
EEA total number of subjects	472

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)	447
From 65 to 84 years	744
85 years and over	22

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled in 221 sites in 35 countries.

Pre-assignment

Screening details:

Stage 1 included atezolizumab+gemcitabine+carboplatin arm or placebo+gemcitabine+carboplatin arm. Participants ineligible for cisplatin-based chemo were enrolled in this stage. Stage 2 included addition of atezolizumab monotherapy arm and allowed participants who were eligible for cisplatin-based chemotherapy.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Blinding implementation details:

In the Atezolizumab+Gemcitabine+Carboplatin/Cisplatin arm, participants received blinded atezolizumab plus open-label platinum-based chemotherapy. In the placebo arm, participants received blinded placebo matched to atezolizumab plus open-label platinum-based chemotherapy. In the Atezolizumab Monotherapy arm, eligible participants received open-label atezolizumab as monotherapy.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo+Gemcitabine+Carboplatin/Cisplatin

Arm description:

Participants received blinded placebo matched to atezolizumab in combination with open-label platinum-based chemotherapy (gemcitabine with either cisplatin or carboplatin).

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

Dosage and administration details:

Carboplatin was administered at doses to achieve area under the concentration-time curve (AUC) of 4.5 milligram per milliliter into minute (mg/mL*min) by IV infusion on Day 1 of each 21-day cycle until investigator-assessed disease progression per RECIST v1.1 or unacceptable toxicity.

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

Dosage and administration details:

Placebo matched to atezolizumab was administered by IV infusion on Day 1 of each 21-day cycle until investigator-assessed disease progression per RECIST v1.1. In specific circumstances treatment may continue beyond disease progression.

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

Dosage and administration details:

Cisplatin was administered at a dose of 70 mg/m^2 by IV infusion on Day 1 of each 21-day cycle until investigator-assessed disease progression per RECIST v1.1 or unacceptable toxicity.

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

Dosage and administration details:

Gemcitabine was administered at a dose of 1000 milligrams per square meter (mg/m^2) by IV infusion on Day 1 and Day 8 of each 21-day cycle, until investigator-assessed disease progression per RECIST v1.1 or unacceptable toxicity.

Arm title	Atezolizumab+Gemcitabine+Carboplatin/Cisplatin

Arm description:

Participants received blinded atezolizumab in combination with open-label platinum-based chemotherapy (gemcitabine with either cisplatin or carboplatin).

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 was administered at a fixed dose of 1200 milligrams (mg) by intravenous (IV) infusion on Day 1 of each 21-day cycle until investigator-assessed disease progression per RECIST v1.1. In specific circumstances treatment may continue beyond disease progression.

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

Dosage and administration details:

Cisplatin was administered at a dose of 70 mg/m^2 by IV infusion on Day 1 of each 21-day cycle until investigator-assessed disease progression per RECIST v1.1 or unacceptable toxicity.

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

Dosage and administration details:

Gemcitabine was administered at a dose of 1000 milligrams per square meter (mg/m^2) by IV infusion on Day 1 and Day 8 of each 21-day cycle, until investigator-assessed disease progression per RECIST v1.1 or unacceptable toxicity.

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

Dosage and administration details:

Carboplatin was administered at doses to achieve area under the concentration-time curve (AUC) of 4.5 milligram per milliliter into minute (mg/mL*min) by IV infusion on Day 1 of each 21-day cycle until investigator-assessed disease progression per RECIST v1.1 or unacceptable toxicity.

Arm title	Atezolizumab Monotherapy

Arm description:

Eligible participants received open-label atezolizumab as monotherapy.

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 was administered at a fixed dose of 1200 milligrams (mg) by intravenous (IV) infusion on Day 1 of each 21-day cycle until investigator-assessed disease progression per RECIST v1.1. In specific circumstances treatment may continue beyond disease progression.

Number of subjects in period 1	Placebo+Gemcitabine+Carboplatin/Cisplatin	Atezolizumab+Gemcitabine+Carboplatin/Cisplatin	Atezolizumab Monotherapy
Started	400	451	362
Completed	0	0	0
Not completed	400	451	362
Consent withdrawn by subject	39	27	23
Protocol Deviation	2	-	-
Ongoing in study	52	84	67
Death	298	327	266
Symptomatic Deterioration	-	1	-
Lost to follow-up	9	12	6

Baseline characteristics

Reporting groups	
Reporting group title	Placebo+Gemcitabine+Carboplatin/Cisplatin
Reporting group description:	
Participants received blinded placebo matched to atezolizumab in combination with open-label platinum-based chemotherapy (gemcitabine with either cisplatin or carboplatin).	
Reporting group title	Atezolizumab+Gemcitabine+Carboplatin/Cisplatin
Reporting group description:	
Participants received blinded atezolizumab in combination with open-label platinum-based chemotherapy (gemcitabine with either cisplatin or carboplatin).	
Reporting group title	Atezolizumab Monotherapy
Reporting group description:	
Eligible participants received open-label atezolizumab as monotherapy.	

Reporting group values	Placebo+Gemcitabine+Carboplatin/Cisplatin	Atezolizumab+Gemcitabine+Carboplatin/Cisplatin	Atezolizumab Monotherapy
Number of subjects	400	451	362
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)	153	152	142
From 65-84 years	240	290	214
85 years and over	7	9	6
Age Continuous Units: Years			
arithmetic mean	66.4	67.5	67.0
standard deviation	± 9.5	± 9.7	± 9.1
Sex: Female, Male Units: Participants			
Female	102	113	82
Male	298	338	280
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	44	41	40
Not Hispanic or Latino	350	402	311
Unknown or Not Reported	6	8	11
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	3	4	2
Asian	85	90	94
Native Hawaiian or Other Pacific Islander	0	0	1

Black or African American	0	6	1
White	305	346	260
More than one race	0	0	1
Unknown or Not Reported	7	5	3

Reporting group values	Total		
Number of subjects	1213		
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)	447		
From 65-84 years	744		
85 years and over	22		
Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Participants			
Female	297		
Male	916		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	125		
Not Hispanic or Latino	1063		
Unknown or Not Reported	25		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	9		
Asian	269		
Native Hawaiian or Other Pacific Islander	1		
Black or African American	7		
White	911		
More than one race	1		
Unknown or Not Reported	15		

End points

End points reporting groups

Reporting group title	Placebo+Gemcitabine+Carboplatin/Cisplatin
Reporting group description:	
Participants received blinded placebo matched to atezolizumab in combination with open-label platinum-based chemotherapy (gemcitabine with either cisplatin or carboplatin).	
Reporting group title	Atezolizumab+Gemcitabine+Carboplatin/Cisplatin
Reporting group description:	
Participants received blinded atezolizumab in combination with open-label platinum-based chemotherapy (gemcitabine with either cisplatin or carboplatin).	
Reporting group title	Atezolizumab Monotherapy
Reporting group description:	
Eligible participants received open-label atezolizumab as monotherapy.	

Primary: Investigator Assessed Progression-Free Survival (PFS) in the Placebo+Gemcitabine+Carboplatin/Cisplatin Arm Versus Atezolizumab +Gemcitabine+Carboplatin/Cisplatin Arm

End point title	Investigator Assessed Progression-Free Survival (PFS) in the Placebo+Gemcitabine+Carboplatin/Cisplatin Arm Versus Atezolizumab +Gemcitabine+Carboplatin/Cisplatin Arm[1]
End point description:	
PFS is defined as the time from randomization to the first documented disease progression as determined by the investigator with the use of RECIST v1.1, or death from any cause, whichever occurs first.	
End point type	Primary
End point timeframe:	
Baseline up to first documented disease progression or death, whichever occurs first (up to approximately 35 months)	
Notes:	
[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Statistical analysis reported as per the specified arms for the end point.	

End point values	Placebo+Gemcitabine+Carboplatin/Cisplatin	Atezolizumab+Gemcitabine+Carboplatin/Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	400	451		
Units: Months				
median (confidence interval 95%)	6.34 (6.24 to 7.00)	8.18 (6.51 to 8.34)		

Statistical analyses

Statistical analysis title	PFS Statistical Analysis

Statistical analysis description:

Stratification factors: Enrollment stage, PD-L1 status, Bajorin risk score/presence of liver metastases, and investigator choice of chemotherapy.

Comparison groups	Placebo+Gemcitabine+Carboplatin/Cisplatin v Atezolizumab+Gemcitabine+Carboplatin/Cisplatin
Number of subjects included in analysis	851
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0073 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	0.96

Notes:

[2] - inverse normal combination

Primary: Overall Survival (OS) in Atezolizumab+Gemcitabine+Carboplatin/Cisplatin Arm Versus Placebo+Gemcitabine+Carboplatin/Cisplatin Arm

End point title	Overall Survival (OS) in Atezolizumab+Gemcitabine+Carboplatin/Cisplatin Arm Versus Placebo+Gemcitabine+Carboplatin/Cisplatin Arm[3]

End point description:

OS is defined as the time from randomization to death due to any cause.

End point type	Primary

End point timeframe:

Baseline until death due to any cause (up to approximately 73 months)

Notes:

[3] - 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: Statistical analysis reported as per the specified arms for the end point.

End point values	Placebo+Gemcitabine+Carboplatin/Cisplatin	Atezolizumab+Gemcitabine+Carboplatin/Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	400	451		
Units: Months				
median (confidence interval 95%)	13.44 (11.99 to 15.34)	16.13 (14.19 to 18.76)		

Statistical analyses

Statistical analysis title	OS Statistical Analysis

Statistical analysis description:

Stratification factors: Enrollment stage, PD-L1 status, Bajorin risk score/presence of liver metastases, and investigator choice of chemotherapy.

Comparison groups	Placebo+Gemcitabine+Carboplatin/Cisplatin v Atezolizumab+Gemcitabine+Carboplatin/Cisplatin

Number of subjects included in analysis	851
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.023 [4]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1

Notes:

[4] - one-sided, inverse normal combination

Primary: Overall Survival (OS) in Atezolizumab Monotherapy Arm Versus Placebo+Gemcitabine+Carboplatin/Cisplatin Arm

End point title	Overall Survival (OS) in Atezolizumab Monotherapy Arm Versus Placebo+Gemcitabine+Carboplatin/Cisplatin Arm[5]

End point description:

OS is defined as the time from randomization to death due to any cause.

End point type	Primary

End point timeframe:

Baseline until death due to any cause (up to approximately 73 months)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analysis reported as per the specified arms for the end point.

End point values	Placebo+Gemcitabine+Carboplatin/Cisplatin	Atezolizumab Monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	359	360		
Units: Months				
median (confidence interval 95%)	13.34 (11.89 to 15.61)	15.21 (13.14 to 17.68)		

Statistical analyses

Statistical analysis title	OS Statistical Analysis
Comparison groups	Placebo+Gemcitabine+Carboplatin/Cisplatin v Atezolizumab Monotherapy
Number of subjects included in analysis	719
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3968 [6]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.98

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.16

Notes:

[6] - one-sided

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)[7]

End point description:

Objective response rate (ORR) is defined as the proportion of participants with a confirmed objective response, either complete response (CR) or partial response (PR), observed on two assessments >= 28 days apart per RECIST v1.1, based on investigator assessment.

End point type	Secondary

End point timeframe:

Baseline up to disease progression, death, or loss of follow-up, whichever occurs first (up to approximately 73 months)

Notes:

[7] - 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: Statistical analysis reported as per the specified arms for the end point.

End point values	Placebo+Gemcitabine+Carboplatin/Cisplatin	Atezolizumab+Gemcitabine+Carboplatin/Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	397	447		
Units: Percentage of Participants				
number (confidence interval 95%)	44.8 (39.87 to 49.88)	48.1 (43.38 to 52.84)		

Statistical analyses

No statistical analyses for this end point

Secondary: IRF-PFS

End point title	IRF-PFS[8]

End point description:

Independent review facility PFS (IRF-PFS) is defined as the time from randomization to the first documented disease progression as determined by blinded independent central review with use of RECIST v1.1, or death due to any cause, whichever occurs first.

End point type	Secondary

End point timeframe:

Randomization to first documented disease progression or death from any cause (up to 35 months)

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analysis reported as per the specified arms for the end point.

End point values	Placebo+Gemcitabine+Carboplatin/Cisplatin	Atezolizumab+Gemcitabine+Carboplatin/Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	400	451		
Units: Months				
number (confidence interval 95%)	6.34 (6.24 to 8.05)	7.10 (6.31 to 8.25)		

Statistical analyses

Statistical analysis title	IRF-PFS Statistical Analysis
Statistical analysis description:	
Stratification factors: Enrollment stage, PD-L1 status, Bajorin risk score/presence of liver metastases, and investigator choice of chemotherapy.	
Comparison groups	Placebo+Gemcitabine+Carboplatin/Cisplatin v Atezolizumab+Gemcitabine+Carboplatin/Cisplatin
Number of subjects included in analysis	851
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0373 [9]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.01

Notes:

[9] - inverse normal combination

Secondary: OS Event Free Rate

End point title	OS Event Free Rate[10]
End point description:	
Overall Survival (OS) Event Free Rate at 1 Year.	
End point type	Secondary
End point timeframe:	
Year 1	

Notes:

[10] - 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: Statistical analysis reported as per the specified arms for the end point.

End point values	Placebo+Gemcitabine+Carboplatin/Cisplatin	Atezolizumab+Gemcitabine+Carboplatin/Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	400	451		
Units: Percentage				
number (confidence interval 95%)	55.00 (49.98 to 60.02)	60.00 (55.39 to 64.61)		

Statistical analyses

Statistical analysis title	OS Event Free Rate Statistical Analysis
Statistical analysis description:	
Stratification factors: Enrollment stage, PD-L1 status, Bajorin risk score/presence of liver metastases, and investigator choice of chemotherapy.	
Comparison groups	Placebo+Gemcitabine+Carboplatin/Cisplatin v Atezolizumab+Gemcitabine+Carboplatin/Cisplatin
Number of subjects included in analysis	851
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1509
Method	Z-test
Parameter estimate	Difference in Event Free Rate
Point estimate	5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.82
upper limit	11.81

Secondary: Duration of response (DOR)

End point title	Duration of response (DOR)[11]
End point description:	
Duration of response (DOR) is defined for participants with an objective response as the time from the first documented objective response to documented disease progression per RECIST v1.1, based on investigator assessment, or death due to any cause, whichever occurs first.	
End point type	Secondary
End point timeframe:	
From first documented objective response (CR or PR) to disease progression, death, or loss of follow-up, whichever occurs first (up to approximately 73 months)	

Notes:

[11] - 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: Statistical analysis reported as per the specified arms for the end point.

End point values	Placebo+Gemcitabine+Carboplatin/Cisplatin	Atezolizumab+Gemcitabine+Carboplatin/Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	215		
Units: Months				
number (confidence interval 95%)	8.15 (6.34 to 8.61)	9.13 (8.02 to 10.64)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Deterioration in Global Health Status as Measured by the EORTC QLQ-C30 Score in the Placebo+Gemcitabine+Carboplatin/Cisplatin Arm Versus Atezolizumab +Gemcitabine+Carboplatin/Cisplatin Arm

End point title	Time to Deterioration in Global Health Status as Measured by the EORTC QLQ-C30 Score in the Placebo+Gemcitabine+Carboplatin/Cisplatin Arm Versus Atezolizumab +Gemcitabine+Carboplatin/Cisplatin Arm[12]

End point description:

Time to deterioration in global health status as measured by the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 in the Placebo+Gemcitabine+Carboplatin/Cisplatin Arm versus Atezolizumab +Gemcitabine+Carboplatin/Cisplatin Arm. Note: 999999=not evaluable.

End point type	Secondary

End point timeframe:

Up to approximately 73 months

Notes:

[12] - 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: Statistical analysis reported as per the specified arms for the end point.

End point values	Placebo+Gemcitabine+Carboplatin/Cisplatin	Atezolizumab+Gemcitabine+Carboplatin/Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	400	451		
Units: Months				
median (confidence interval 95%)	12.06 (8.28 to 20.24)	32.07 (18.40 to 999999)		

Statistical analyses

Statistical analysis title	Global Health Status Statistical Analysis

Statistical analysis description:

Strata are: Enrollment Stage, PD-L1 Status, BAJORIN Risk Factor Score and Stratum 4 for all participants.

Comparison groups	Placebo+Gemcitabine+Carboplatin/Cisplatin v Atezolizumab+Gemcitabine+Carboplatin/Cisplatin

Number of subjects included in analysis	851
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0542
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1

Secondary: PFS Event Free Rate

End point title	PFS Event Free Rate[13]

End point description:

Progression Free Survival (PFS) Event Free Rate at Year 1

End point type	Secondary

End point timeframe:

Year 1

Notes:

[13] - 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: Statistical analysis reported as per the specified arms for the end point.

End point values	Placebo+Gemcitabine+Carboplatin/Cisplatin	Atezolizumab+Gemcitabine+Carboplatin/Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	400	451		
Units: Percentage				
number (confidence interval 95%)	22.17 (17.93 to 26.42)	30.47 (26.00 to 34.93)		

Statistical analyses

Statistical analysis title	PFS Event Free Rate Statistical Analysis

Statistical analysis description:

Stratification factors: Enrollment stage, PD-L1 status, Bajorin risk score/presence of liver metastases, and investigator choice of chemotherapy.

Comparison groups	Placebo+Gemcitabine+Carboplatin/Cisplatin v Atezolizumab+Gemcitabine+Carboplatin/Cisplatin

Number of subjects included in analysis	851
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0083
Method	Z-test
Parameter estimate	Difference in Event Free Rate
Point estimate	-8.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.45
upper limit	-2.13

Secondary: Time to Deterioration in Global Health Status as Measured by the EORTC QLQ-C30 Score in the Placebo+Gemcitabine+Carboplatin/Cisplatin Arm Versus Atezolizumab Monotherapy Arm

End point title	Time to Deterioration in Global Health Status as Measured by the EORTC QLQ-C30 Score in the Placebo+Gemcitabine+Carboplatin/Cisplatin Arm Versus Atezolizumab Monotherapy Arm[14]

End point description:

Time to deterioration in global health status as measured by the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 in the Placebo+Gemcitabine+Carboplatin/Cisplatin Arm versus Atezolizumab Monotherapy Arm. Note: 999999=not evaluable.

End point type	Secondary

End point timeframe:

Up to approximately 73 months

Notes:

[14] - 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: Statistical analysis reported as per the specified arms for the end point.

End point values	Placebo+Gemcitabine+Carboplatin/Cisplatin	Atezolizumab Monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	359	360		
Units: Months				
median (confidence interval 95%)	12.02 (8.08 to 20.24)	23.20 (8.31 to 999999)		

Statistical analyses

Statistical analysis title	Global Health Status Statistical Analysis

Statistical analysis description:

Strata are: PD-L1 Status, BAJORIN Risk Factor Score and Stratum 4 for all participants.

Comparison groups	Placebo+Gemcitabine+Carboplatin/Cisplatin v Atezolizumab Monotherapy

Number of subjects included in analysis	719
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6139
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.19

Secondary: Time to Deterioration in Physical Function as Measured by the EORTC QLQ-C30 Score in the Placebo+Gemcitabine+Carboplatin/Cisplatin Arm Versus Atezolizumab Monotherapy Arm

End point title	Time to Deterioration in Physical Function as Measured by the EORTC QLQ-C30 Score in the Placebo+Gemcitabine+Carboplatin/Cisplatin Arm Versus Atezolizumab Monotherapy Arm[15]

End point description:

Median time to deterioration in physical function as measured by the QLQ-C30 in the Placebo+Gemcitabine+Carboplatin/Cisplatin Arm versus Atezolizumab Monotherapy Arm. Note: 999999=not evaluable.

End point type	Secondary

End point timeframe:

Up to approximately 73 months

Notes:

[15] - 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: Statistical analysis reported as per the specified arms for the end point.

End point values	Placebo+Gemcitabine+Carboplatin/Cisplatin	Atezolizumab Monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	359	360		
Units: Months				
median (confidence interval 95%)	16.10 (8.08 to 22.57)	9.23 (6.24 to 17.48)		

Statistical analyses

Statistical analysis title	Physical Function Statistical Analysis

Statistical analysis description:

Strata are: Enrollment Stage, PD-L1 Status, BAJORIN Risk Factor Score and Stratum 4 for all participants.

Comparison groups	Placebo+Gemcitabine+Carboplatin/Cisplatin v Atezolizumab Monotherapy

Number of subjects included in analysis	719
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0241
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.03
upper limit	1.62

Secondary: Time to Deterioration in Physical Function as Measured by the EORTC QLQ-C30 Score in the Placebo+Gemcitabine+Carboplatin/Cisplatin Arm Versus Atezolizumab +Gemcitabine+Carboplatin/Cisplatin Arm

End point title	Time to Deterioration in Physical Function as Measured by the EORTC QLQ-C30 Score in the Placebo+Gemcitabine+Carboplatin/Cisplatin Arm Versus Atezolizumab +Gemcitabine+Carboplatin/Cisplatin Arm[16]

End point description:

Median time to deterioration in physical function as measured by the QLQ-C30 in the Placebo+Gemcitabine+Carboplatin/Cisplatin Arm versus Atezolizumab +Gemcitabine+Carboplatin/Cisplatin Arm.

End point type	Secondary

End point timeframe:

Up to approximately 73 months

Notes:

[16] - 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: Statistical analysis reported as per the specified arms for the end point.

End point values	Placebo+Gemcitabine+Carboplatin/Cisplatin	Atezolizumab+Gemcitabine+Carboplatin/Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	400	451		
Units: Months				
median (confidence interval 95%)	15.74 (8.28 to 22.57)	16.39 (9.07 to 26.68)		

Statistical analyses

Statistical analysis title	Physical Function Statistical Analysis

Statistical analysis description:

Strata are: Enrollment Stage, PD-L1 Status, BAJORIN Risk Factor Score and Stratum 4 for all participants.

Comparison groups	Placebo+Gemcitabine+Carboplatin/Cisplatin v Atezolizumab+Gemcitabine+Carboplatin/Cisplatin

Number of subjects included in analysis	851
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.554
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.32

Secondary: Minimum Atezolizumab Serum Concentration

End point title	Minimum Atezolizumab Serum Concentration[17]

End point description:

Minimum atezolizumab serum concentration.

End point type	Secondary

End point timeframe:

Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1, Cycle 8 Day 1, Cycle 16 Day 1, Cycle 24 Day 1, Cycle 32 Day 1, Day 120 post dose of last blinded (LB) atezolizumab treatment, and study drug early discontinuation

Notes:

[17] - 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: Statistical analysis reported as per the specified arms for the end point.

End point values	Atezolizumab+ Gemcitabine+Carboplatin/Cisplatin	Atezolizumab Monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	382	297		
Units: µg/ mL				
arithmetic mean (standard deviation)				
Cycle 2 Day 1 (n=382, 297)	79.8 (± 52.5)	80.2 (± 46.0)		
Cycle 3 Day 1 (n=365, 245)	122 (± 47.2)	129 (± 66.0)		
Cycle 4 Day 1 (n=321, 183)	153 (± 70.4)	157 (± 63.4)		
Cycle 8 Day 1 (n=194, 104)	216 (± 96.8)	193 (± 79.8)		
Cycle 16 Day 1 (n=40, 50)	235 (± 103)	220 (± 79.8)		
Cycle 24 Day 1 (n=36, 29)	244 (± 75.7)	233 (± 92.5)		
Cycle 32 Day 1 (n=17, 9)	259 (± 97.2)	258 (± 60.5)		
Day 120 Post Dose of LB Atezo Trt (n=67, 64)	18.8 (± 36.9)	9.53 (± 12.7)		
Study Drug Early Discontinuation (n=194, 148)	154 (± 102)	124 (± 83.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Atezolizumab Serum Concentration

End point title	Maximum Atezolizumab Serum Concentration[18]

End point description:

Maximum atezolizumab serum concentration.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1

Notes:

[18] - 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: Statistical analysis reported as per the specified arms for the end point.

End point values	Atezolizumab+ Gemcitabine+Carboplatin/Cisplatin	Atezolizumab Monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	394	309		
Units: µg/ mL				
arithmetic mean (standard deviation)	379 (± 125)	390 (± 129)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage of Participants With Anti-Therapeutic (Anti-Atezolizumab) Antibodies (ATAs)[19]

End point description:

Percentage of Participants with Anti-Therapeutic (Anti-Atezolizumab) Antibodies (ATAs)

End point type	Secondary

End point timeframe:

Up to approximately 35 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: Statistical analysis reported as per the specified arms for the end point.

End point values	Atezolizumab+ Gemcitabine+Carboplatin/Cisplatin	Atezolizumab Monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	434	341		
Units: Percentage of participants				
number (not applicable)				

Baseline evaluable participants (n=434, 341)	1.2	0.9		
Post-baseline evaluable participants (n=421, 319)	19.7	26.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator-Assessed Progression-Free Survival (INV-PFS) in Participants Treated with Atezolizumab Montotherapy Compared With Placebo+Gemcitabine+Carboplatin/Cisplatin

End point title	Investigator-Assessed Progression-Free Survival (INV-PFS) in Participants Treated with Atezolizumab Montotherapy Compared With Placebo+Gemcitabine+Carboplatin/Cisplatin[20]

End point description:

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

End point type	Secondary

End point timeframe:

Baseline up to disease progression, death, or loss of follow-up, whichever occurs first (assessed at baseline, every 9 weeks for 54 weeks and every 12 weeks thereafter up to 35 months)

Notes:

[20] - 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: Statistical analysis reported as per the specified arms for the end point.

End point values	Placebo+Gemcitabine+Carboplatin/Cisplatin	Atezolizumab Monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	359	360		
Units: Months				
median (confidence interval 95%)	6.31 (6.24 to 6.74)	2.69 (2.20 to 4.04)		

Statistical analyses

Statistical analysis title	INV-PFS Statistical Analysis

Statistical analysis description:

Stratification factors: PD-L1 status and Bajorin risk score/presence of liver metastases and investigator choice of chemotherapy.

Comparison groups	Placebo+Gemcitabine+Carboplatin/Cisplatin v Atezolizumab Monotherapy

Number of subjects included in analysis	719
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.19
upper limit	1.69

Secondary: Percentage of Participants with Adverse Events (AEs) Assessed Using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0

End point title	Percentage of Participants with Adverse Events (AEs) Assessed Using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0

End point description:

End point type	Secondary

End point timeframe:

Baseline up to 90 months

End point values	Placebo+Gemcitabine+Carboplatin/Cisplatin	Atezolizumab+Gemcitabine+Carboplatin/Cisplatin	Atezolizumab Monotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[21]	0[22]	0[23]	
Units: Percentage of Participants				

Notes:

[21] - This will be reported at the time of final results posting.

[22] - This will be reported at the time of final results posting.

[23] - This will be reported at the time of final results posting.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first study drug to the data cutoff date: 31 August 2022 (up to approximately 73 months)

Adverse event reporting additional description:

The safety population was defined as participants who received any amount of any component of study treatment. Participants were analyzed according to the treatment received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Placebo+Gemcitabine+Carboplatin/Cisplatin

Reporting group description:

Participants received blinded placebo matched to atezolizumab in combination with open-label platinum-based chemotherapy (gemcitabine with either cisplatin or carboplatin).

Reporting group title	Atezolizumab Monotherapy

Reporting group description:

Eligible participants received open-label atezolizumab as monotherapy.

Reporting group title	Atezolizumab+Gemcitabine+Carboplatin/Cisplatin

Reporting group description:

Participants received blinded atezolizumab in combination with open-label platinum-based chemotherapy (gemcitabine with either cisplatin or carboplatin).

Serious adverse events	Placebo+Gemcitabine+Carboplatin/Cisplatin	Atezolizumab Monotherapy	Atezolizumab+Gemcitabine+Carboplatin/Cisplatin
Total subjects affected by serious adverse events			
subjects affected / exposed	196 / 389 (50.39%)	163 / 354 (46.05%)	243 / 454 (53.52%)
number of deaths (all causes)	304	267	340
number of deaths resulting from adverse events	4	3	9
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lipoma			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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 neoplasm malignant			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Malignant pleural effusion			

subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal carcinoma			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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 associated fever			
subjects affected / exposed	0 / 389 (0.00%)	2 / 354 (0.56%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Embolism			
subjects affected / exposed	2 / 389 (0.51%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism venous			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Venous thrombosis			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Venous thrombosis limb			

subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral venous disease			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Leriche syndrome			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Jugular vein thrombosis			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemic shock			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hypertension			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	1 / 389 (0.26%)	1 / 354 (0.28%)	0 / 454 (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
Surgical and medical procedures			
Nephrostomy			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Euthanasia			

subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nephrostomy tube removal			
subjects affected / exposed	2 / 389 (0.51%)	1 / 354 (0.28%)	0 / 454 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 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	2 / 389 (0.51%)	3 / 354 (0.85%)	4 / 454 (0.88%)
occurrences causally related to treatment / all	2 / 2	1 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Death			
subjects affected / exposed	7 / 389 (1.80%)	2 / 354 (0.56%)	6 / 454 (1.32%)
occurrences causally related to treatment / all	1 / 7	0 / 2	0 / 6
deaths causally related to treatment / all	1 / 7	0 / 2	0 / 6
Fatigue			
subjects affected / exposed	4 / 389 (1.03%)	2 / 354 (0.56%)	3 / 454 (0.66%)
occurrences causally related to treatment / all	4 / 4	0 / 2	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Malaise			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	2 / 454 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucosal inflammation			

subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Accidental death			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suprapubic pain			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Sudden cardiac death			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	12 / 389 (3.08%)	9 / 354 (2.54%)	18 / 454 (3.96%)
occurrences causally related to treatment / all	4 / 13	4 / 10	8 / 19
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	2 / 389 (0.51%)	4 / 354 (1.13%)	5 / 454 (1.10%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			

subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaphylactic reaction			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Hypersensitivity			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Vaginal haemorrhage			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Acute pulmonary oedema			

subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 389 (0.51%)	1 / 354 (0.28%)	2 / 454 (0.44%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 389 (0.26%)	5 / 354 (1.41%)	7 / 454 (1.54%)
occurrences causally related to treatment / all	0 / 1	1 / 5	4 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Dyspnoea exertional			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	1 / 389 (0.26%)	3 / 354 (0.85%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	1 / 1	3 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Pulmonary embolism			
subjects affected / exposed	4 / 389 (1.03%)	1 / 354 (0.28%)	7 / 454 (1.54%)
occurrences causally related to treatment / all	0 / 4	0 / 1	2 / 8
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Pneumothorax			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	3 / 389 (0.77%)	4 / 354 (1.13%)	7 / 454 (1.54%)
occurrences causally related to treatment / all	3 / 3	5 / 5	7 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Pleurisy			

subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
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	1 / 389 (0.26%)	2 / 354 (0.56%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	2 / 389 (0.51%)	0 / 354 (0.00%)	0 / 454 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	1 / 1
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Confusional state			
subjects affected / exposed	1 / 389 (0.26%)	1 / 354 (0.28%)	0 / 454 (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
Completed suicide			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Anxiety			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Product issues			

Device occlusion			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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 dislocation			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	12 / 389 (3.08%)	0 / 354 (0.00%)	14 / 454 (3.08%)
occurrences causally related to treatment / all	18 / 18	0 / 0	23 / 23
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	6 / 389 (1.54%)	0 / 354 (0.00%)	3 / 454 (0.66%)
occurrences causally related to treatment / all	3 / 7	0 / 0	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test abnormal			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Neutrophil count decreased			

subjects affected / exposed	7 / 389 (1.80%)	0 / 354 (0.00%)	3 / 454 (0.66%)
occurrences causally related to treatment / all	8 / 8	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Transaminases increased			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Weight decreased			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
White blood cell count decreased			
subjects affected / exposed	3 / 389 (0.77%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	4 / 4	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Incisional hernia			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
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 / 389 (0.00%)	1 / 354 (0.28%)	2 / 454 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			

subjects affected / exposed	1 / 389 (0.26%)	1 / 354 (0.28%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Infusion related reaction			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple fractures			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative adhesion			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural intestinal perforation			

subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	2 / 454 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stoma prolapse			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stoma site haemorrhage			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stoma site pain			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Subdural haematoma			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Road traffic accident			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Transfusion reaction			

subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Unintentional medical device removal			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract stoma complication			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Urostomy complication			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Congenital cystic kidney disease			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	2 / 454 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 389 (0.26%)	1 / 354 (0.28%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Cardiac failure			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	3 / 454 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Cardiac failure acute			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Atrioventricular block complete			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Atrial fibrillation			
subjects affected / exposed	1 / 389 (0.26%)	1 / 354 (0.28%)	2 / 454 (0.44%)
occurrences causally related to treatment / all	1 / 1	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Angina unstable			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Acute myocardial infarction			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Acute coronary syndrome			
subjects affected / exposed	1 / 389 (0.26%)	2 / 354 (0.56%)	3 / 454 (0.66%)
occurrences causally related to treatment / all	1 / 1	0 / 3	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Cardiopulmonary failure			

subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular dysfunction			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Ventricular fibrillation			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Supraventricular tachycardia			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus arrest			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Myocardial infarction			
subjects affected / exposed	2 / 389 (0.51%)	0 / 354 (0.00%)	2 / 454 (0.44%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Autoimmune encephalopathy			

subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Central nervous system haemorrhage			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemianopia			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Headache			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Haemorrhage intracranial			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Encephalopathy			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	2 / 454 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolic stroke			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Intraventricular haemorrhage			

subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Demyelination			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Cerebrovascular accident			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	2 / 454 (0.44%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cerebral ischaemia			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cerebral haemorrhage			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cerebral artery embolism			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Dysaesthesia			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
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 cerebral infarction			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Ischaemic stroke			

subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	3 / 454 (0.66%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbosacral radiculopathy			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Migraine			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Miller Fisher syndrome			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Myasthenia gravis			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myasthenic syndrome			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuralgia			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Paraparesis			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Presyncope			

subjects affected / exposed	1 / 389 (0.26%)	1 / 354 (0.28%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 389 (0.00%)	2 / 354 (0.56%)	3 / 454 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 2	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tremor			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	2 / 454 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	2 / 454 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematotoxicity			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Febrile neutropenia			

subjects affected / exposed	9 / 389 (2.31%)	0 / 354 (0.00%)	14 / 454 (3.08%)
occurrences causally related to treatment / all	8 / 9	0 / 0	15 / 15
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	19 / 389 (4.88%)	4 / 354 (1.13%)	30 / 454 (6.61%)
occurrences causally related to treatment / all	22 / 26	1 / 4	29 / 34
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	4 / 389 (1.03%)	0 / 354 (0.00%)	6 / 454 (1.32%)
occurrences causally related to treatment / all	4 / 4	0 / 0	6 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	4 / 389 (1.03%)	0 / 354 (0.00%)	8 / 454 (1.76%)
occurrences causally related to treatment / all	5 / 5	0 / 0	10 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Myelosuppression			
subjects affected / exposed	3 / 389 (0.77%)	0 / 354 (0.00%)	3 / 454 (0.66%)
occurrences causally related to treatment / all	7 / 7	0 / 0	6 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymph node pain			
subjects affected / exposed	0 / 389 (0.00%)	2 / 354 (0.56%)	0 / 454 (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
Thrombocytosis			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	22 / 389 (5.66%)	1 / 354 (0.28%)	21 / 454 (4.63%)
occurrences causally related to treatment / all	28 / 28	1 / 1	30 / 30
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Ear and labyrinth disorders			
Deafness			

subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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 disorders			
Enterocutaneous fistula			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	3 / 389 (0.77%)	3 / 354 (0.85%)	4 / 454 (0.88%)
occurrences causally related to treatment / all	3 / 3	1 / 3	4 / 4
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 389 (0.26%)	1 / 354 (0.28%)	0 / 454 (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
Colitis			
subjects affected / exposed	1 / 389 (0.26%)	1 / 354 (0.28%)	0 / 454 (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
Autoimmune pancreatitis			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Gastritis			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Abdominal pain			
subjects affected / exposed	0 / 389 (0.00%)	2 / 354 (0.56%)	2 / 454 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal incarcerated hernia			

subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal hernia			
subjects affected / exposed	1 / 389 (0.26%)	1 / 354 (0.28%)	0 / 454 (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
Enterovesical fistula			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Abdominal pain upper			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids thrombosed			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Hiatus hernia			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileal ulcer			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			

subjects affected / exposed	3 / 389 (0.77%)	3 / 354 (0.85%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	1 / 3	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	3 / 389 (0.77%)	8 / 354 (2.26%)	3 / 454 (0.66%)
occurrences causally related to treatment / all	0 / 3	0 / 9	2 / 3
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Rectal obstruction			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mechanical ileus			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Obstruction gastric			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Pancreatitis			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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 acute			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Large intestinal obstruction			

subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Small intestinal obstruction			
subjects affected / exposed	1 / 389 (0.26%)	2 / 354 (0.56%)	2 / 454 (0.44%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	2 / 389 (0.51%)	0 / 354 (0.00%)	0 / 454 (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
Volvulus			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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	3 / 389 (0.77%)	0 / 354 (0.00%)	5 / 454 (1.10%)
occurrences causally related to treatment / all	3 / 3	0 / 0	5 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Cholecystitis			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	2 / 454 (0.44%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			

subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	1 / 1
Hepatic function abnormal			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune hepatitis			
subjects affected / exposed	0 / 389 (0.00%)	2 / 354 (0.56%)	0 / 454 (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
Jaundice cholestatic			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Hypertransaminasaemia			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis toxic			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Skin and subcutaneous tissue disorders			
Skin necrosis			

subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pruritus			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermatomyositis			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Dermal cyst			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Renal and urinary disorders			
Bladder pain			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder tamponade			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Autoimmune nephritis			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anuria			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			

subjects affected / exposed	12 / 389 (3.08%)	8 / 354 (2.26%)	15 / 454 (3.30%)
occurrences causally related to treatment / all	7 / 12	0 / 8	9 / 16
deaths causally related to treatment / all	0 / 0	0 / 1	1 / 1
Calculus urinary			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
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 kidney disease			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	10 / 389 (2.57%)	13 / 354 (3.67%)	10 / 454 (2.20%)
occurrences causally related to treatment / all	0 / 11	2 / 13	5 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	3 / 389 (0.77%)	3 / 354 (0.85%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pollakiuria			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Proteinuria			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	3 / 454 (0.66%)
occurrences causally related to treatment / all	0 / 0	1 / 1	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal disorder			

subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	2 / 389 (0.51%)	8 / 354 (2.26%)	3 / 454 (0.66%)
occurrences causally related to treatment / all	2 / 2	2 / 8	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Renal impairment			
subjects affected / exposed	1 / 389 (0.26%)	2 / 354 (0.56%)	5 / 454 (1.10%)
occurrences causally related to treatment / all	0 / 1	0 / 2	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Renal injury			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Renal tubular injury			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal artery stenosis			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction			
subjects affected / exposed	3 / 389 (0.77%)	2 / 354 (0.56%)	7 / 454 (1.54%)
occurrences causally related to treatment / all	0 / 3	1 / 2	0 / 7
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	2 / 389 (0.51%)	4 / 354 (1.13%)	5 / 454 (1.10%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary fistula			

subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Ureteric obstruction			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 389 (0.26%)	1 / 354 (0.28%)	0 / 454 (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
Hypopituitarism			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Hypophysitis			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adrenal insufficiency			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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

Arthritis			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	1 / 389 (0.26%)	1 / 354 (0.28%)	0 / 454 (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
Fistula			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Flank pain			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Groin pain			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Myositis			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	3 / 389 (0.77%)	0 / 354 (0.00%)	3 / 454 (0.66%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoporotic fracture			

subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
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 in extremity			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Pathological fracture			
subjects affected / exposed	1 / 389 (0.26%)	1 / 354 (0.28%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Bacterial sepsis			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial infection			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	2 / 454 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	1 / 389 (0.26%)	1 / 354 (0.28%)	0 / 454 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	2 / 389 (0.51%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal infection			

subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Campylobacter infection			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	2 / 454 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	2 / 454 (0.44%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Emphysematous pyelonephritis			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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 infection			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fungal infection			

subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Escherichia urinary tract infection			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Endocarditis			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalitis			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected skin ulcer			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	2 / 389 (0.51%)	3 / 354 (0.85%)	2 / 454 (0.44%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			

subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Kidney infection			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Klebsiella sepsis			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle abscess			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Nasopharyngitis			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Norovirus infection			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orchitis			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Pharyngitis streptococcal			

subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
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			
subjects affected / exposed	8 / 389 (2.06%)	8 / 354 (2.26%)	21 / 454 (4.63%)
occurrences causally related to treatment / all	4 / 8	3 / 8	7 / 23
deaths causally related to treatment / all	0 / 0	1 / 2	0 / 2
Pneumonia aspiration			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia pneumococcal			
subjects affected / exposed	0 / 389 (0.00%)	2 / 354 (0.56%)	0 / 454 (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
Pseudomonal bacteraemia			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Pulmonary sepsis			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Pyelonephritis			
subjects affected / exposed	3 / 389 (0.77%)	3 / 354 (0.85%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	1 / 3	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	1 / 389 (0.26%)	1 / 354 (0.28%)	4 / 454 (0.88%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			

subjects affected / exposed	1 / 389 (0.26%)	2 / 354 (0.56%)	3 / 454 (0.66%)
occurrences causally related to treatment / all	0 / 1	0 / 2	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 389 (0.26%)	1 / 354 (0.28%)	0 / 454 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	2 / 389 (0.51%)	3 / 354 (0.85%)	2 / 454 (0.44%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 2	0 / 3	0 / 2
Skin infection			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Subcutaneous abscess			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Tracheobronchitis			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Tuberculosis			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Sepsis			
subjects affected / exposed	7 / 389 (1.80%)	1 / 354 (0.28%)	7 / 454 (1.54%)
occurrences causally related to treatment / all	2 / 8	0 / 1	3 / 8
deaths causally related to treatment / all	0 / 1	0 / 1	1 / 1
Urinary tract infection			

subjects affected / exposed	30 / 389 (7.71%)	22 / 354 (6.21%)	41 / 454 (9.03%)
occurrences causally related to treatment / all	8 / 42	2 / 23	11 / 57
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection bacterial			
subjects affected / exposed	2 / 389 (0.51%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection fungal			
subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	0 / 454 (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
Urinary tract infection staphylococcal			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	4 / 389 (1.03%)	5 / 354 (1.41%)	3 / 454 (0.66%)
occurrences causally related to treatment / all	0 / 4	1 / 5	1 / 3
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 1
Vascular device infection			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cachexia			

subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Hyperglycaemia			
subjects affected / exposed	1 / 389 (0.26%)	1 / 354 (0.28%)	2 / 454 (0.44%)
occurrences causally related to treatment / all	0 / 1	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Dehydration			
subjects affected / exposed	2 / 389 (0.51%)	1 / 354 (0.28%)	2 / 454 (0.44%)
occurrences causally related to treatment / all	0 / 2	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic metabolic decompensation			
subjects affected / exposed	1 / 389 (0.26%)	0 / 354 (0.00%)	0 / 454 (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
Hypercalcaemia			
subjects affected / exposed	0 / 389 (0.00%)	2 / 354 (0.56%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercreatininaemia			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	0 / 389 (0.00%)	2 / 354 (0.56%)	0 / 454 (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
Hypoglycaemia			

subjects affected / exposed	0 / 389 (0.00%)	1 / 354 (0.28%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypomagnesaemia			
subjects affected / exposed	0 / 389 (0.00%)	0 / 354 (0.00%)	1 / 454 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	2 / 389 (0.51%)	1 / 354 (0.28%)	0 / 454 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	2 / 389 (0.51%)	1 / 354 (0.28%)	0 / 454 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 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	Placebo+Gemcitabine+Carboplatin/Cisplatin	Atezolizumab Monotherapy	Atezolizumab+Gemcitabine+Carboplatin/Cisplatin
Total subjects affected by non-serious adverse events			
subjects affected / exposed	379 / 389 (97.43%)	300 / 354 (84.75%)	441 / 454 (97.14%)
Vascular disorders			
Hypertension			
subjects affected / exposed	31 / 389 (7.97%)	21 / 354 (5.93%)	45 / 454 (9.91%)
occurrences (all)	41	26	62
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	98 / 389 (25.19%)	51 / 354 (14.41%)	133 / 454 (29.30%)
occurrences (all)	156	76	207
Fatigue			

subjects affected / exposed	122 / 389 (31.36%)	64 / 354 (18.08%)	134 / 454 (29.52%)
occurrences (all)	182	83	185
Malaise			
subjects affected / exposed	24 / 389 (6.17%)	6 / 354 (1.69%)	18 / 454 (3.96%)
occurrences (all)	35	6	34
Oedema peripheral			
subjects affected / exposed	56 / 389 (14.40%)	41 / 354 (11.58%)	53 / 454 (11.67%)
occurrences (all)	67	56	68
Pyrexia			
subjects affected / exposed	68 / 389 (17.48%)	43 / 354 (12.15%)	122 / 454 (26.87%)
occurrences (all)	113	57	172
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	33 / 389 (8.48%)	25 / 354 (7.06%)	43 / 454 (9.47%)
occurrences (all)	43	28	54
Cough			
subjects affected / exposed	38 / 389 (9.77%)	30 / 354 (8.47%)	58 / 454 (12.78%)
occurrences (all)	46	49	67
Psychiatric disorders			
Insomnia			
subjects affected / exposed	34 / 389 (8.74%)	19 / 354 (5.37%)	36 / 454 (7.93%)
occurrences (all)	37	20	39
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	10 / 389 (2.57%)	22 / 354 (6.21%)	26 / 454 (5.73%)
occurrences (all)	15	27	33
Aspartate aminotransferase increased			
subjects affected / exposed	17 / 389 (4.37%)	22 / 354 (6.21%)	46 / 454 (10.13%)
occurrences (all)	28	25	61
Alanine aminotransferase increased			
subjects affected / exposed	26 / 389 (6.68%)	24 / 354 (6.78%)	47 / 454 (10.35%)
occurrences (all)	32	27	57
Blood creatinine increased			
subjects affected / exposed	45 / 389 (11.57%)	28 / 354 (7.91%)	66 / 454 (14.54%)
occurrences (all)	64	33	89
Weight decreased			

subjects affected / exposed	25 / 389 (6.43%)	23 / 354 (6.50%)	30 / 454 (6.61%)
occurrences (all)	25	23	35
White blood cell count decreased			
subjects affected / exposed	59 / 389 (15.17%)	1 / 354 (0.28%)	62 / 454 (13.66%)
occurrences (all)	166	1	144
Platelet count decreased			
subjects affected / exposed	138 / 389 (35.48%)	5 / 354 (1.41%)	132 / 454 (29.07%)
occurrences (all)	331	7	350
Neutrophil count decreased			
subjects affected / exposed	129 / 389 (33.16%)	0 / 354 (0.00%)	119 / 454 (26.21%)
occurrences (all)	344	0	331
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	23 / 389 (5.91%)	6 / 354 (1.69%)	17 / 454 (3.74%)
occurrences (all)	25	8	19
Headache			
subjects affected / exposed	34 / 389 (8.74%)	24 / 354 (6.78%)	42 / 454 (9.25%)
occurrences (all)	43	35	65
Dizziness			
subjects affected / exposed	39 / 389 (10.03%)	18 / 354 (5.08%)	45 / 454 (9.91%)
occurrences (all)	51	19	59
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	117 / 389 (30.08%)	12 / 354 (3.39%)	183 / 454 (40.31%)
occurrences (all)	297	13	378
Anaemia			
subjects affected / exposed	257 / 389 (66.07%)	67 / 354 (18.93%)	308 / 454 (67.84%)
occurrences (all)	481	81	488
Leukopenia			
subjects affected / exposed	64 / 389 (16.45%)	0 / 354 (0.00%)	63 / 454 (13.88%)
occurrences (all)	192	0	131
Neutropenia			
subjects affected / exposed	148 / 389 (38.05%)	2 / 354 (0.56%)	215 / 454 (47.36%)
occurrences (all)	421	2	509
Gastrointestinal disorders			

Vomiting			
subjects affected / exposed	106 / 389 (27.25%)	33 / 354 (9.32%)	122 / 454 (26.87%)
occurrences (all)	175	41	178
Nausea			
subjects affected / exposed	181 / 389 (46.53%)	43 / 354 (12.15%)	202 / 454 (44.49%)
occurrences (all)	317	53	329
Dyspepsia			
subjects affected / exposed	22 / 389 (5.66%)	5 / 354 (1.41%)	20 / 454 (4.41%)
occurrences (all)	28	10	21
Diarrhoea			
subjects affected / exposed	73 / 389 (18.77%)	42 / 354 (11.86%)	94 / 454 (20.70%)
occurrences (all)	96	57	142
Constipation			
subjects affected / exposed	111 / 389 (28.53%)	67 / 354 (18.93%)	140 / 454 (30.84%)
occurrences (all)	149	74	186
Abdominal pain			
subjects affected / exposed	37 / 389 (9.51%)	22 / 354 (6.21%)	44 / 454 (9.69%)
occurrences (all)	54	27	54
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	49 / 389 (12.60%)	2 / 354 (0.56%)	33 / 454 (7.27%)
occurrences (all)	50	2	35
Pruritus			
subjects affected / exposed	33 / 389 (8.48%)	41 / 354 (11.58%)	84 / 454 (18.50%)
occurrences (all)	38	65	122
Rash			
subjects affected / exposed	43 / 389 (11.05%)	27 / 354 (7.63%)	91 / 454 (20.04%)
occurrences (all)	52	32	117
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	51 / 389 (13.11%)	47 / 354 (13.28%)	73 / 454 (16.08%)
occurrences (all)	65	55	102
Dysuria			
subjects affected / exposed	20 / 389 (5.14%)	20 / 354 (5.65%)	29 / 454 (6.39%)
occurrences (all)	26	23	41
Endocrine disorders			

Hypothyroidism			
subjects affected / exposed	12 / 389 (3.08%)	30 / 354 (8.47%)	44 / 454 (9.69%)
occurrences (all)	12	31	47
Hyperthyroidism			
subjects affected / exposed	6 / 389 (1.54%)	18 / 354 (5.08%)	35 / 454 (7.71%)
occurrences (all)	6	20	39
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	30 / 389 (7.71%)	21 / 354 (5.93%)	35 / 454 (7.71%)
occurrences (all)	37	24	43
Myalgia			
subjects affected / exposed	23 / 389 (5.91%)	23 / 354 (6.50%)	27 / 454 (5.95%)
occurrences (all)	35	30	29
Back pain			
subjects affected / exposed	45 / 389 (11.57%)	33 / 354 (9.32%)	56 / 454 (12.33%)
occurrences (all)	56	39	66
Arthralgia			
subjects affected / exposed	44 / 389 (11.31%)	39 / 354 (11.02%)	57 / 454 (12.56%)
occurrences (all)	56	55	79
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	61 / 389 (15.68%)	58 / 354 (16.38%)	89 / 454 (19.60%)
occurrences (all)	91	101	134
Upper respiratory tract infection			
subjects affected / exposed	19 / 389 (4.88%)	18 / 354 (5.08%)	30 / 454 (6.61%)
occurrences (all)	26	22	36
Nasopharyngitis			
subjects affected / exposed	20 / 389 (5.14%)	18 / 354 (5.08%)	33 / 454 (7.27%)
occurrences (all)	25	26	44
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	12 / 389 (3.08%)	14 / 354 (3.95%)	26 / 454 (5.73%)
occurrences (all)	21	33	30
Hyponatraemia			
subjects affected / exposed	16 / 389 (4.11%)	9 / 354 (2.54%)	30 / 454 (6.61%)
occurrences (all)	21	10	37

Hypomagnesaemia			
subjects affected / exposed	22 / 389 (5.66%)	8 / 354 (2.26%)	26 / 454 (5.73%)
occurrences (all)	27	11	31
Hypoalbuminaemia			
subjects affected / exposed	15 / 389 (3.86%)	19 / 354 (5.37%)	21 / 454 (4.63%)
occurrences (all)	24	20	27
Hyperkalaemia			
subjects affected / exposed	29 / 389 (7.46%)	13 / 354 (3.67%)	24 / 454 (5.29%)
occurrences (all)	39	17	39
Decreased appetite			
subjects affected / exposed	119 / 389 (30.59%)	69 / 354 (19.49%)	143 / 454 (31.50%)
occurrences (all)	165	72	212

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 September 2016	Protocol has been amended to include the addition of a third treatment arm to the study of atezolizumab as monotherapy. The study design was modified to include participants who were eligible for a cisplatin-containing regimen. Participants who were ineligible for cisplatin were continued to be enrolled. A primary efficacy objective was added: To evaluate the efficacy of atezolizumab monotherapy compared with placebo plus platinum-based chemotherapy on the basis of OS. A secondary efficacy objective was added: Investigator-assessed PFS in participants treated with atezolizumab monotherapy compared with participants treated with placebo plus platinum-based chemotherapy.
30 April 2018	Protocol has been amended to reflect that randomization of new participants to all three arms will continue in a 1:1:1 manner regardless of PD-L1 expression status; however, for participants randomized to Atezolizumab monotherapy arm, PD-L1 expression status will be unblinded to the investigator and participants at the time of randomization. The protocol has been updated to reflect the following treatment options for new participants randomized to Atezolizumab Monotherapy arm: PD-L1 status will be unblinded to the investigator and participant at the time of randomization. Participants with a PD-L1 expression status of IC2/3 will receive atezolizumab monotherapy. Participants with a PD-L1 expression status of IC0 or IC1 will receive open-label atezolizumab plus platinum (carboplatin or cisplatin) and gemcitabine chemotherapy instead of atezolizumab monotherapy. Participants with PD-L1 expression status of IC0 or IC1 are recommended to continue with atezolizumab monotherapy and participants with PD-L1 expression status of IC2/3 will continue receiving atezolizumab monotherapy. Secondary Efficacy Objective has been updated to reflect the addition of an Independent Review Facility-progression-free survival (PFS) endpoint, defined as the time from randomization to the first documented disease progression as determined by blinded independent central review with use of RECIST v1.1, or death due to any cause, whichever occurs first.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported