Clinical trial results:
A Phase III, Open-Label, Multicenter, Randomized Study of Atezolizumab (Anti-PD-L1 Antibody) Versus Observation as Adjuvant Therapy in Patients With High-Risk Muscle-Invasive Urothelial Carcinoma After Surgical Resection

Summary

EudraCT number	2014-005603-25
Trial protocol	ES FI CZ DE BE NL GB FR GR PL
Global end of trial date	

Results information

Result version number	v1
This version publication date	06 November 2020
First version publication date	06 November 2020

Trial information

Trial identification

Sponsor protocol code	WO29636

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02450331
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	30 November 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 November 2019
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this global Phase III, open-label, randomized, controlled trial is to evaluate the efficacy and safety of adjuvant treatment with atezolizumab compared with observation in patients with muscle-invasive UC, who are at high risk for recurrence following resection.

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

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 6
Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	Canada: 31
Country: Number of subjects enrolled	Switzerland: 3
Country: Number of subjects enrolled	China: 38
Country: Number of subjects enrolled	Czech Republic: 15
Country: Number of subjects enrolled	Germany: 24
Country: Number of subjects enrolled	Spain: 45
Country: Number of subjects enrolled	Finland: 14
Country: Number of subjects enrolled	France: 46
Country: Number of subjects enrolled	United Kingdom: 24
Country: Number of subjects enrolled	Greece: 17
Country: Number of subjects enrolled	Israel: 30
Country: Number of subjects enrolled	Italy: 54
Country: Number of subjects enrolled	Japan: 55
Country: Number of subjects enrolled	Korea, Republic of: 23
Country: Number of subjects enrolled	Netherlands: 35
Country: Number of subjects enrolled	Poland: 17
Country: Number of subjects enrolled	Russian Federation: 33
Country: Number of subjects enrolled	Serbia: 11
Country: Number of subjects enrolled	Turkey: 32
Country: Number of subjects enrolled	Taiwan: 9
Country: Number of subjects enrolled	Ukraine: 24

Country: Number of subjects enrolled	United States: 210
Worldwide total number of subjects	809
EEA total number of subjects	304

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)	338
From 65 to 84 years	467
85 years and over	4

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study included male and female participants aged >=18 years with Eastern Cooperative Oncology Group (ECOG) performance status <=2 who have histologically confirmed muscle-invasive UC of the bladder or upper urinary tract.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Observation

Arm description:

Participants underwent observation starting on Day 1 for 16 cycles (up to 1 year).

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Atezolizumab

Arm description:

Participants received intravenous (IV) atezolizumab on Day 1 of each 21-day cycle for 16 cycles (up to 1 year).

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 intravenously at a dose of 1200 milligrams (mg) on Day 1 of each 21-day cycle for 16 cycles (up to 1 year).

Number of subjects in period 1	Observation	Atezolizumab
Started	403	406
Completed	0	0
Not completed	403	406
Adverse event, serious fatal	120	114
Consent withdrawn by subject	50	39
In Survival follow-up	45	38
In Disease recurrence follow-up	179	208
Lost to follow-up	9	7

Baseline characteristics

Reporting groups	
Reporting group title	Observation
Reporting group description:	
Participants underwent observation starting on Day 1 for 16 cycles (up to 1 year).	
Reporting group title	Atezolizumab
Reporting group description:	
Participants received intravenous (IV) atezolizumab on Day 1 of each 21-day cycle for 16 cycles (up to 1 year).	

Reporting group values	Observation	Atezolizumab	Total
Number of subjects	403	406	809
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)	169	169	338
From 65-84 years	232	235	467
85 years and over	2	2	4
Age Continuous Units: Years			
arithmetic mean	65.9	66.0	
standard deviation	± 9.3	± 9.0	-
Sex: Female, Male Units: Participants			
Female	87	84	171
Male	316	322	638
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	68	64	132
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	3	3	6
White	307	320	627
Other	4	6	10
Unknown	21	12	33
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	9	16	25
Not Hispanic or Latino	357	369	726
Unknown or Not Reported	37	21	58

End points

End points reporting groups

Reporting group title	Observation
Reporting group description:	
Participants underwent observation starting on Day 1 for 16 cycles (up to 1 year).	
Reporting group title	Atezolizumab
Reporting group description:	
Participants received intravenous (IV) atezolizumab on Day 1 of each 21-day cycle for 16 cycles (up to 1 year).	

Primary: Disease-Free Survival (DFS), as Assessed by Investigator

End point title	Disease-Free Survival (DFS), as Assessed by Investigator
End point description:	
DFS is defined as the time from randomization to the time of first occurrence of a DFS event. DFS events include: local (pelvic) recurrence of UC (including soft tissue and regional lymph nodes); urinary tract recurrence of UC (including all pathological stages and grades); distant metastasis of UC; or death from any cause. Tumor assessment will be performed using radiographic evaluations.	
End point type	Primary
End point timeframe:	
Randomization up to first occurrence of DFS event (up to approximately 50 months)	

End point values	Observation	Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	403	406		
Units: Months				
median (confidence interval 95%)	16.6 (11.2 to 24.8)	19.4 (15.9 to 24.8)		

Statistical analyses

Statistical analysis title	Statistical Analysis for DFS
Comparison groups	Atezolizumab v Observation
Number of subjects included in analysis	809
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2446
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.892

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.735
upper limit	1.081

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival is defined as the time from randomization to the date of death from any cause, regardless of whether the death occurs during study treatment or following treatment discontinuation. Note: 999999 = not estimatable.

End point type	Secondary

End point timeframe:

Randomization until death due to any cause (up to approximately 50 months)

End point values	Observation	Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	403	406		
Units: Months				
median (confidence interval 95%)	999999 (38.2 to 999999)	999999 (999999 to 999999)		

Statistical analyses

Statistical analysis title	Statistical Analysis for OS
Comparison groups	Atezolizumab v Observation
Number of subjects included in analysis	809
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1951
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.846
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.657
upper limit	1.09

Secondary: Disease-Specific Survival (DSS), as Assessed by Investigator

End point title	Disease-Specific Survival (DSS), as Assessed by Investigator

End point description:

DSS is defined as the time from randomization until the date of death from UC. Note: 999999 = not estimatable.

End point type	Secondary

End point timeframe:

Randomization until death due to UC (up to approximately 50 months)

End point values	Observation	Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	403	406		
Units: Months				
median (confidence interval 95%)	999999 (999999 to 999999)	999999 (999999 to 999999)		

Statistical analyses

Statistical analysis title	Statistical Analysis for DSS
Comparison groups	Atezolizumab v Observation
Number of subjects included in analysis	809
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2235
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.836
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.626
upper limit	1.116

Secondary: Distant Metastasis-Free Survival (DMFS)

End point title	Distant Metastasis-Free Survival (DMFS)

End point description:

DMFS is defined as the time from randomization to the date of diagnosis of distant (that is, non-locoregional) metastases or death from any cause. Tumor assessment will be performed using radiographic evaluations. Note: 999999 = not estimatable.

End point type	Secondary

End point timeframe:

Randomization up to diagnosis of distant metastases or death from any cause (up to approximately 50 months)

End point values	Observation	Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	403	406		
Units: Months				
median (confidence interval 95%)	31.1 (21.7 to 41.4)	27.5 (22.6 to 999999)		

Statistical analyses

Statistical analysis title	Statistical Analysis for DMFS
Comparison groups	Atezolizumab v Observation
Number of subjects included in analysis	809
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4291
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.918
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.743
upper limit	1.134

Secondary: Non-Urinary Tract Recurrence-Free Survival (NURFS)

End point title	Non-Urinary Tract Recurrence-Free Survival (NURFS)

End point description:

NURFS is defined as the time from randomization to the time of first occurrence of a NURFS event. NURFS events include: local (pelvic) recurrence of UC (including soft tissue and regional lymph nodes); distant metastasis of UC; or death from any cause. Tumor assessment will be performed using radiographic evaluations.

End point type	Secondary

End point timeframe:

Randomization up to time of first occurrence of a NURFS event (up to approximately 50 months)

End point values	Observation	Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	403	406		
Units: Months				
median (confidence interval 95%)	19.5 (12.3 to 27.7)	22.1 (17.2 to 27.6)		

Statistical analyses

Statistical analysis title	Statistical Analysis for NURFS
Comparison groups	Atezolizumab v Observation
Number of subjects included in analysis	809
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1994
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.879
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.722
upper limit	1.07

Secondary: Percentage of Participants with Adverse Events (AEs)

End point title	Percentage of Participants with Adverse Events (AEs)
End point description:	
Percentage of participants with at least one Adverse Event.	
End point type	Secondary
End point timeframe:	
Screening up to approximately 50 months	

End point values	Observation	Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	397	390		
Units: Percentage of Participants				
number (not applicable)	78.8	94.4		

Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage of Participants With Anti-Therapeutic Antibodies (ATAs) to Atezolizumab[1]

End point description:

Percentage of participants with anti-therapeutic antibodies to atezolizumab.

End point type	Secondary

End point timeframe:

Baseline up to approximately 50 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: No statistical analysis for this end point.

End point values	Atezolizumab			
Subject group type	Reporting group			
Number of subjects analysed	375			
Units: Percentage of Participants				
number (not applicable)	29.3			

Statistical analyses

No statistical analyses for this end point

Secondary: EuroQol 5-Dimension 5-Level (EQ-5D-5L) Visual Analogue Scale Score

End point title	EuroQol 5-Dimension 5-Level (EQ-5D-5L) Visual Analogue Scale Score

End point description:

The EQ-5D-5L is a generic preference-based HRQoL questionnaire that provides a single index value for health status and is used to inform pharmacoeconomic evaluations and to measure general health status. Visual analog scale (VAS) allows the patient to indicate, on a scale of 0-100, how his or her health is on the day of assessment, with 100 being the "best imaginable health state" and 0 being the "worst imaginable health state."

End point type	Secondary

End point timeframe:

Day 1 of Cycle 1 up to approximately 50 months (Cycle length = 21 days)

End point values	Observation	Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	403	406		
Units: Score on scale				
arithmetic mean (standard deviation)				
Cycle 1 Day 1	77.41 (± 15.74)	78.89 (± 16.13)		
Cycle 3 Day 1	78.64 (± 15.73)	81.05 (± 14.96)		

Cycle 5 Day 1	79.94 (± 16.32)	81.95 (± 14.32)		
Cycle 7 Day 1	80.81 (± 16.37)	82.39 (± 14.43)		
Cycle 9 Day 1	81.24 (± 15.70)	82.06 (± 15.34)		
Cycle 11 Day 1	81.39 (± 17.02)	82.81 (± 14.96)		
Cycle 13 Day 1	81.39 (± 16.99)	82.59 (± 14.81)		
Cycle 15 Day 1	82.78 (± 16.01)	83.67 (± 14.47)		
Treatment Discontinuation	82.68 (± 16.19)	81.91 (± 15.96)		

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Observed Serum Atezolizumab Concentration (Cmin)

End point title	Minimum Observed Serum Atezolizumab Concentration

End point description:

Minimum observed serum atezolizumab concentration (Cmin) prior to infusion on Day 1 of Cycles 1, 2, 3, and 4; every 8 cycles starting on Cycle 8; at treatment discontinuation; and at 120 days after the last dose of atezolizumab.

End point type	Secondary

End point timeframe:

Pre-dose (Hour 0) on Day 1 of Cycles 1, 2, 3, 4, every 8 cycles from Cycle 8, at treatment discontinuation, 120 days after treatment discontinuation (up to approximately 50 months)

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis for this end point.

End point values	Atezolizumab			
Subject group type	Reporting group			
Number of subjects analysed	380			
Units: µg/mL				
arithmetic mean (standard deviation)				
Cycle 2 Day 1	78.4 (± 25.2)			
Cycle 3 Day 1	125 (± 46.0)			
Cycle 4 Day 1	152 (± 71.1)			
Cycle 8 Day 1	203 (± 92.0)			
Cycle 16 Day 1	225 (± 106)			
Day 120 Post Last Dose MPDL3280A	15.9 (± 19.5)			
Study Drug or Study Phase Comp or Early Disc	164 (± 106)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Serum Atezolizumab Concentration (Cmax)

End point title	Maximum Observed Serum Atezolizumab Concentration

End point description:

Maximum observed serum atezolizumab concentration (Cmax) after infusion on Day 1 of Cycle 1.

End point type	Secondary

End point timeframe:

Day 1 of Cycle 1 (Cycle length = 21 days)

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: No statistical analysis for this end point.

End point values	Atezolizumab			
Subject group type	Reporting group			
Number of subjects analysed	300			
Units: µg/mL				
arithmetic mean (standard deviation)	365 (± 121)			

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: 30 November 2019 (up to 50 months)

Adverse event reporting additional description:

The safety-evaluable population for atezolizumab was defined as patients who received at least one dose of atezolizumab. The safety-evaluable population for observation was defined as patients randomized to observation who had at least one post-baseline safety assessment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	OBSERVATION

Reporting group description:

Participants underwent observation starting on Day 1 for 16 cycles (up to 1 year).

Reporting group title	ATEZOLIZUMAB

Reporting group description:

Participants received intravenous (IV) atezolizumab on Day 1 of each 21-day cycle for 16 cycles (up to 1 year).

Serious adverse events	OBSERVATION	ATEZOLIZUMAB	
Total subjects affected by serious adverse events			
subjects affected / exposed	71 / 397 (17.88%)	122 / 390 (31.28%)	
number of deaths (all causes)	124	114	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			
subjects affected / exposed	1 / 397 (0.25%)	0 / 390 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	1 / 397 (0.25%)	0 / 390 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Laryngeal squamous cell carcinoma			
subjects affected / exposed	1 / 397 (0.25%)	0 / 390 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lung adenocarcinoma			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			
subjects affected / exposed	1 / 397 (0.25%)	0 / 390 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tumour of ampulla of Vater			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Arteriosclerosis			
subjects affected / exposed	1 / 397 (0.25%)	0 / 390 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	3 / 397 (0.76%)	0 / 390 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 397 (0.25%)	0 / 390 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 397 (0.25%)	0 / 390 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypotension			
subjects affected / exposed	1 / 397 (0.25%)	0 / 390 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocele			

subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia pain			
subjects affected / exposed	1 / 397 (0.25%)	0 / 390 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 397 (0.25%)	3 / 390 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 3	
Hyperthermia			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lithiasis			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			

subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	4 / 397 (1.01%)	11 / 390 (2.82%)	
occurrences causally related to treatment / all	0 / 4	6 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic immune activation			
subjects affected / exposed	0 / 397 (0.00%)	2 / 390 (0.51%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Female genital tract fistula			
subjects affected / exposed	2 / 397 (0.50%)	0 / 390 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Asthma			

subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 397 (0.25%)	0 / 390 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 397 (0.00%)	3 / 390 (0.77%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	5 / 397 (1.26%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	1 / 397 (0.25%)	0 / 390 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device occlusion			
subjects affected / exposed	1 / 397 (0.25%)	0 / 390 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Incision site impaired healing			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	0 / 397 (0.00%)	2 / 390 (0.51%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Post procedural haemorrhage			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Stoma obstruction			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomal hernia			
subjects affected / exposed	1 / 397 (0.25%)	0 / 390 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric anastomosis complication			
subjects affected / exposed	1 / 397 (0.25%)	0 / 390 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urostomy complication			
subjects affected / exposed	1 / 397 (0.25%)	0 / 390 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 397 (0.00%)	2 / 390 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 397 (0.25%)	0 / 390 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			

subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 397 (0.25%)	0 / 390 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated neuropathy			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 397 (0.25%)	0 / 390 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	1 / 397 (0.25%)	0 / 390 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 397 (0.50%)	0 / 390 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 397 (0.00%)	4 / 390 (1.03%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 397 (0.50%)	0 / 390 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovesical fistula			
subjects affected / exposed	1 / 397 (0.25%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 397 (0.00%)	5 / 390 (1.28%)	
occurrences causally related to treatment / all	0 / 0	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			

subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernial eventration			
subjects affected / exposed	1 / 397 (0.25%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 397 (0.25%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated enterocolitis			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	2 / 397 (0.50%)	4 / 390 (1.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	0 / 397 (0.00%)	2 / 390 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical ileus			
subjects affected / exposed	1 / 397 (0.25%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 397 (0.25%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			

subjects affected / exposed	1 / 397 (0.25%)	0 / 390 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	2 / 397 (0.50%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestine ulcer			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 397 (0.25%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	0 / 397 (0.00%)	2 / 390 (0.51%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			

subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic haematoma			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver disorder			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 397 (1.01%)	8 / 390 (2.05%)	
occurrences causally related to treatment / all	0 / 4	3 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune nephritis			

subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysuria			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 397 (0.25%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephritis			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal injury			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric obstruction			
subjects affected / exposed	1 / 397 (0.25%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric stenosis			

subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 397 (0.25%)	0 / 390 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	1 / 397 (0.25%)	2 / 390 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinoma			
subjects affected / exposed	1 / 397 (0.25%)	0 / 390 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vesicoureteric reflux			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophysitis			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothyroidism			

subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin pain			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 397 (0.00%)	2 / 390 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	1 / 397 (0.25%)	0 / 390 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bacteraemia			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 397 (0.25%)	0 / 390 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot infection			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	1 / 397 (0.25%)	0 / 390 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 397 (0.25%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			
subjects affected / exposed	1 / 397 (0.25%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			

subjects affected / exposed	1 / 397 (0.25%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroborreliosis			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 397 (0.50%)	4 / 390 (1.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyelonephritis			
subjects affected / exposed	9 / 397 (2.27%)	12 / 390 (3.08%)	
occurrences causally related to treatment / all	0 / 11	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 397 (0.25%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis chronic			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal abscess			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory tract infection			

subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 397 (0.25%)	3 / 390 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 1	
Septic shock			
subjects affected / exposed	1 / 397 (0.25%)	0 / 390 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	19 / 397 (4.79%)	30 / 390 (7.69%)	
occurrences causally related to treatment / all	0 / 22	1 / 41	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	1 / 397 (0.25%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	3 / 397 (0.76%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			

subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	1 / 397 (0.25%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 397 (0.00%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 397 (0.25%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 397 (0.25%)	0 / 390 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	2 / 397 (0.50%)	1 / 390 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	OBSERVATION	ATEZOLIZUMAB	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	232 / 397 (58.44%)	324 / 390 (83.08%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	7 / 397 (1.76%)	24 / 390 (6.15%)	
occurrences (all)	8	32	
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 397 (1.26%)	20 / 390 (5.13%)	
occurrences (all)	6	25	
Blood alkaline phosphatase increased			
subjects affected / exposed	8 / 397 (2.02%)	20 / 390 (5.13%)	
occurrences (all)	8	29	
Blood creatinine increased			
subjects affected / exposed	17 / 397 (4.28%)	37 / 390 (9.49%)	
occurrences (all)	20	42	
Nervous system disorders			
Dizziness			
subjects affected / exposed	11 / 397 (2.77%)	20 / 390 (5.13%)	
occurrences (all)	11	22	
Headache			
subjects affected / exposed	8 / 397 (2.02%)	35 / 390 (8.97%)	
occurrences (all)	8	39	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	32 / 397 (8.06%)	42 / 390 (10.77%)	
occurrences (all)	34	53	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	16 / 397 (4.03%)	35 / 390 (8.97%)	
occurrences (all)	16	41	
Chills			
subjects affected / exposed	7 / 397 (1.76%)	23 / 390 (5.90%)	
occurrences (all)	9	25	
Fatigue			

subjects affected / exposed	42 / 397 (10.58%)	89 / 390 (22.82%)	
occurrences (all)	49	118	
Oedema peripheral			
subjects affected / exposed	23 / 397 (5.79%)	34 / 390 (8.72%)	
occurrences (all)	26	38	
Pyrexia			
subjects affected / exposed	30 / 397 (7.56%)	71 / 390 (18.21%)	
occurrences (all)	43	90	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	29 / 397 (7.30%)	31 / 390 (7.95%)	
occurrences (all)	32	39	
Constipation			
subjects affected / exposed	39 / 397 (9.82%)	51 / 390 (13.08%)	
occurrences (all)	40	60	
Diarrhoea			
subjects affected / exposed	25 / 397 (6.30%)	81 / 390 (20.77%)	
occurrences (all)	29	103	
Nausea			
subjects affected / exposed	20 / 397 (5.04%)	52 / 390 (13.33%)	
occurrences (all)	21	60	
Vomiting			
subjects affected / exposed	14 / 397 (3.53%)	26 / 390 (6.67%)	
occurrences (all)	16	34	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	23 / 397 (5.79%)	47 / 390 (12.05%)	
occurrences (all)	23	60	
Dyspnoea			
subjects affected / exposed	7 / 397 (1.76%)	27 / 390 (6.92%)	
occurrences (all)	7	33	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	2 / 397 (0.50%)	29 / 390 (7.44%)	
occurrences (all)	2	30	
Pruritus			

subjects affected / exposed	10 / 397 (2.52%)	92 / 390 (23.59%)	
occurrences (all)	14	113	
Rash			
subjects affected / exposed	5 / 397 (1.26%)	38 / 390 (9.74%)	
occurrences (all)	6	48	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 397 (0.00%)	35 / 390 (8.97%)	
occurrences (all)	0	38	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	24 / 397 (6.05%)	43 / 390 (11.03%)	
occurrences (all)	26	48	
Back pain			
subjects affected / exposed	44 / 397 (11.08%)	26 / 390 (6.67%)	
occurrences (all)	54	31	
Myalgia			
subjects affected / exposed	6 / 397 (1.51%)	21 / 390 (5.38%)	
occurrences (all)	8	30	
Pain in extremity			
subjects affected / exposed	9 / 397 (2.27%)	22 / 390 (5.64%)	
occurrences (all)	9	29	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	18 / 397 (4.53%)	21 / 390 (5.38%)	
occurrences (all)	19	27	
Urinary tract infection			
subjects affected / exposed	59 / 397 (14.86%)	63 / 390 (16.15%)	
occurrences (all)	84	88	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	20 / 397 (5.04%)	45 / 390 (11.54%)	
occurrences (all)	21	54	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 September 2015	Protocol was amended under inclusion criteria with the removal of cytology as one of the methods to diagnose muscle-invasive transitional cell carcinoma (TCC) of the bladder given that histopathology is the standard. Under the exclusion criteria, the requirement of participants to be taken off denosumab has been removed. Because participants in this adjuvant trial would not have bone disease at baseline, there is not a need for denosumab to treat cancer-related bone disease.
04 April 2016	Protocol was amended under inclusion criteria. High risk participants with muscle-invasive urothelial carcinoma (UC) of the upper urinary tract, or participants with carcinoma in situ at the distal ureteral or urethral margin after cystectomy, have been added to the eligible study population given that those participants may benefit from study treatment. The criteria for participants who have received prior neoadjuvant chemotherapy have been clarified to describe participants who have received at least two cycles of a platinum-containing regimen. The requirement for tumor specimens for central testing of PD-L1 expression prior to study enrollment has been clarified to include samples from cystectomy (or radical tumor resection for patients with muscle-invasive UC of the renal pelvis or ureters) or lymph node dissection. The randomization window after cystectomy has been increased from 12 weeks to 14 weeks to allow additional time for potential eligible participants to recover from surgery.
14 July 2016	Protocol was amended to revise the study design from a diagnostically selected (PD-L1 IHC score of IC2/3 only) study to include all participants regardless of PD-L1 status as a result of data from the ongoing Phase II IMvigor210 study showing that treatment-naive cisplatin-ineligible participants with advanced urothelial carcinoma may benefit from first-line atezolizumab treatment regardless of PD-L1 status. The total sample size has been increased from 440 to 700. Non-urinary tract recurrence-free survival (NURFS) has been added as a secondary efficacy objective to distinguish non-urinary tract recurrence from urinary tract recurrence.
04 October 2017	Protocol was amended to increase the total sample size from 700 to 800. The end of study projection has been updated from 79 months from first patient in (FPI) to 95 months from FPI to accommodate the increased sample size. Tumor stage M0 has been added to the tumor staging inclusion criterion to further clarify that participants with metastatic disease at the time of surgical resection are ineligible for the study.
19 November 2018	Protocol was amended to include an update to the timing of the analysis of the primary endpoint of disease-free survival (DFS) in order to ensure a minimum of 12 months of follow-up for efficacy and safety for the study population.
13 April 2020	Protocol was amended to include following the primary analysis, participants who are in Years 1-3 or Years 2-3, as applicable,of the study and are in disease recurrence follow-up may now be assessed for recurrence every 24 weeks. EQ-5D-5L assessments are no longer required for participants who are in disease recurrence follow-up or for participants who have had a DFS event.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported