Clinical trial results:
A Phase III, Open-Label, Multicenter, Randomized Study to Investigate the Efficacy and Safety of Atezolizumab (Anti-PD-L1 Antibody) Compared With Chemotherapy in Patients With Locally Advanced or Metastatic Urothelial Bladder Cancer After Failure With Platinum-Containing Chemotherapy

Summary

EudraCT number	2014-003231-19
Trial protocol	CZ IT PL SI SE DE GB HU PT NL FI NO DK BE AT ES FR GR RO
Global end of trial date	

Results information

Result version number	v1
This version publication date	29 March 2018
First version publication date	29 March 2018

Trial information

Trial identification

Sponsor protocol code	GO29294

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02302807
WHO universal trial number (UTN)	-
Other trial identifiers	Other Sponsor ID: IMvigor211

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	13 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 March 2017
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this Phase III, open-label, multicenter, randomized study was to investigate the efficacy of atezolizumab (Anti-PD-L1 Antibody) compared with chemotherapy in subjects with locally advanced or metastatic urothelial bladder cancer after failure with platinum-containing chemotherapy.

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	13 January 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: 19
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Belgium: 20
Country: Number of subjects enrolled	Canada: 47
Country: Number of subjects enrolled	Denmark: 9
Country: Number of subjects enrolled	France: 176
Country: Number of subjects enrolled	Spain: 110
Country: Number of subjects enrolled	United Kingdom: 84
Country: Number of subjects enrolled	Italy: 73
Country: Number of subjects enrolled	Japan: 56
Country: Number of subjects enrolled	Germany: 54
Country: Number of subjects enrolled	Czech Republic: 8
Country: Number of subjects enrolled	Slovakia: 7
Country: Number of subjects enrolled	Russian Federation: 6
Country: Number of subjects enrolled	Hungary: 5
Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	Serbia: 5
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	Finland: 3
Country: Number of subjects enrolled	United States: 24
Country: Number of subjects enrolled	Korea, Republic of: 31
Country: Number of subjects enrolled	Turkey: 16
Country: Number of subjects enrolled	Taiwan: 26

Country: Number of subjects enrolled	Poland: 15
Country: Number of subjects enrolled	Portugal: 15
Country: Number of subjects enrolled	Romania: 13
Country: Number of subjects enrolled	Netherlands: 52
Country: Number of subjects enrolled	Greece: 22
Country: Number of subjects enrolled	Switzerland: 25
Worldwide total number of subjects	931
EEA total number of subjects	676

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)	371
From 65 to 84 years	558
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Recruitment included in 198 centers in 29 countries: France, Spain, Great Britain, Italy, Japan, Germany, Netherlands, Canada, Korea, Taiwan, Switzerland, United States, Greece, Belgium, Australia, Turkey, Poland, Portugal, Romania, Denmark, Czechoslovakia, Slovakia, Russia, Hungary, Norway, Serbia, Sweden, Finland, and Austria.

Pre-assignment

Screening details:

Subjects in the study included: histologically or cytologically documented locally advanced or metastatic UBC; and disease progression during or following treatment with at least one platinum containing regimen for inoperable, locally advanced or metastatic UBC or disease recurrence.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Chemotherapy (Vinflunine, Paclitaxel, or Docetaxel)

Arm description:

Subjects randomized to the chemotherapy arm received vinflunine, paclitaxel, or docetaxel per the investigator's choice. Vinflunine 320 milligrams per square meter (mg/m^2), paclitaxel 175 mg/m^2, or docetaxel 75 mg/m^2 was administered intravenously on Day 1 of each 21-day cycle until disease progression per standard RECIST v1.1 or unacceptable toxicity.

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

Dosage and administration details:

Subjects randomized to the chemotherapy arm received vinflunine, per the investigator's choice. Vinflunine 320 milligrams per square meter (mg/m^2) was administered intravenously on Day 1 of each 21-day cycle until disease progression per standard RECIST v1.1 or unacceptable toxicity.

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

Dosage and administration details:

Subjects randomized to the chemotherapy received paclitaxel, per the investigator's choice. Paclitaxel 175 mg/m^2 was administered intravenously on Day 1 of each 21-day cycle until disease progression per standard RECIST v1.1 or unacceptable toxicity.

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

Dosage and administration details:

Subjects randomized to the chemotherapy arm received docetaxel per the investigator's choice. Docetaxel 75 mg/m^2 was administered intravenously on Day 1 of each 21-day cycle until disease

progression per standard RECIST v1.1 or unacceptable toxicity.

Arm title	Atezolizumab

Arm description:

Atezolizumab was administered intravenously at a fixed dose of 1200 milligrams (mg) on Day 1 of each 21-day cycle. Subjects received atezolizumab as long as they continued to experience clinical benefit in the opinion of the investigator until unacceptable toxicity or symptomatic deterioration attributed to disease progression as determined by the investigator

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

Dosage and administration details:

Atezolizumab was administered intravenously at a fixed dose of 1200 milligrams (mg) on Day 1 of each 21-day cycle. Subjects received atezolizumab as long as they continued to experience clinical benefit in the opinion of the investigator until unacceptable toxicity or symptomatic deterioration attributed to disease progression as determined by the investigator

Number of subjects in period 1	Chemotherapy (Vinflunine, Paclitaxel, or Docetaxel)	Atezolizumab
Started	464	467
Received Treatment	443	459
Completed	89	133
Not completed	375	334
Adverse event, serious fatal	345	322
Consent withdrawn by subject	27	9
Lost to follow-up	3	3

Baseline characteristics

Reporting groups	
Reporting group title	Chemotherapy (Vinflunine, Paclitaxel, or Docetaxel)

Reporting group description:

Subjects randomized to the chemotherapy arm received vinflunine, paclitaxel, or docetaxel per the investigator's choice. Vinflunine 320 milligrams per square meter (mg/m^2), paclitaxel 175 mg/m^2, or docetaxel 75 mg/m^2 was administered intravenously on Day 1 of each 21-day cycle until disease progression per standard RECIST v1.1 or unacceptable toxicity.

Reporting group title	Atezolizumab

Reporting group description:

Atezolizumab was administered intravenously at a fixed dose of 1200 milligrams (mg) on Day 1 of each 21-day cycle. Subjects received atezolizumab as long as they continued to experience clinical benefit in the opinion of the investigator until unacceptable toxicity or symptomatic deterioration attributed to disease progression as determined by the investigator

Reporting group values	Chemotherapy (Vinflunine, Paclitaxel, or Docetaxel)	Atezolizumab	Total
Number of subjects	464	467	931
Age categorical Units: Subjects			
Age Continuous Units: Years			
arithmetic mean	66.1	65.9	
standard deviation	± 9.3	± 9.6	-
Sex: Female, Male Units: Subjects			
Female	103	110	213
Male	361	357	718
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	55	63	118
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	1	3
White	336	335	671
More than one race	1	0	1
Unknown or Not Reported	70	68	138
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	16	13	29
Not Hispanic or Latino	368	363	731
Unknown or Not Reported	80	91	171

End points

End points reporting groups

Reporting group title	Chemotherapy (Vinflunine, Paclitaxel, or Docetaxel)

Reporting group description:

Subjects randomized to the chemotherapy arm received vinflunine, paclitaxel, or docetaxel per the investigator's choice. Vinflunine 320 milligrams per square meter (mg/m^2), paclitaxel 175 mg/m^2, or docetaxel 75 mg/m^2 was administered intravenously on Day 1 of each 21-day cycle until disease progression per standard RECIST v1.1 or unacceptable toxicity.

Reporting group title	Atezolizumab

Reporting group description:

Atezolizumab was administered intravenously at a fixed dose of 1200 milligrams (mg) on Day 1 of each 21-day cycle. Subjects received atezolizumab as long as they continued to experience clinical benefit in the opinion of the investigator until unacceptable toxicity or symptomatic deterioration attributed to disease progression as determined by the investigator

Subject analysis set title	IC2/3 Chemotherapy Subset 1
Subject analysis set type	Sub-group analysis

Subject analysis set description:

ITT population, defined as all randomized subjects, irrespective of whether the assigned treatment was actually received, with PD-L1 immunohistochemistry (IHC) score of IC2/3 analyzed for Overall Survival and Progression-Free Survival

Subject analysis set title	IC2/3 Atezolizumab Subset 1
Subject analysis set type	Sub-group analysis

Subject analysis set description:

ITT population, defined as all randomized subjects, irrespective of whether the assigned treatment was actually received, with PD-L1 immunohistochemistry (IHC) score of IC2/3 analyzed for Overall Survival and Progression-Free Survival

Subject analysis set title	IC1/2/3 Chemotherapy Subset 1
Subject analysis set type	Sub-group analysis

Subject analysis set description:

ITT population, defined as all randomized subjects, irrespective of whether the assigned treatment was actually received, with PD-L1 immunohistochemistry (IHC) score of IC1/2/3 analyzed for Overall Survival and Progression-Free Survival

Subject analysis set title	IC1/2/3 Atezolizumab Subset 1
Subject analysis set type	Sub-group analysis

Subject analysis set description:

ITT population, defined as all randomized subjects, irrespective of whether the assigned treatment was actually received, with PD-L1 immunohistochemistry (IHC) score of IC1/2/3 analyzed for Overall Survival and Progression-Free Survival

Subject analysis set title	IC2/3 Chemotherapy Subset 2
Subject analysis set type	Sub-group analysis

Subject analysis set description:

PD-L1 immunohistochemistry (IHC) score of IC2/3 analyzed for Objective Response Rate. ORR analyses was performed on all randomized subjects who had measureable disease at baseline.

Subject analysis set title	IC2/3 Atezolizumab Subset 2
Subject analysis set type	Sub-group analysis

Subject analysis set description:

PD-L1 immunohistochemistry (IHC) score of IC2/3 analyzed for Objective Response Rate. ORR analyses was performed on all randomized subjects who had measureable disease at baseline.

Subject analysis set title	IC1/2/3 Chemotherapy Subset 2
Subject analysis set type	Sub-group analysis

Subject analysis set description:

PD-L1 immunohistochemistry (IHC) score of IC1/2/3 analyzed for Objective Response Rate. ORR analyses was performed on all randomized subjects who had measureable disease at baseline.

Subject analysis set title	IC1/2/3 Atezolizumab Subset 2
Subject analysis set type	Sub-group analysis

Subject analysis set description:

PD-L1 immunohistochemistry (IHC) score of IC1/2/3 analyzed for Objective Response Rate. ORR analyses was performed on all randomized subjects who had measureable disease at baseline. PD-L1 immunohistochemistry (IHC) score of IC1/2/3 analyzed for Adverse Events. Safety analyses was performed on all randomized subjects who received any amount of study treatment, with patients grouped according to whether any amount of atezolizumab was received including the case when atezolizumab was received in error.

Subject analysis set title	IC2/3 Chemotherapy Subset 3
Subject analysis set type	Sub-group analysis

Subject analysis set description:

PD-L1 immunohistochemistry (IHC) score of IC2/3 analyzed for Duration of Response. DOR analyses was performed on the subset of subjects who achieved an objective response.

Subject analysis set title	IC2/3 Atezolizumab Subset 3
Subject analysis set type	Sub-group analysis

Subject analysis set description:

PD-L1 immunohistochemistry (IHC) score of IC2/3 analyzed for Duration of Response. DOR analyses was performed on the subset of subjects who achieved an objective response.

Subject analysis set title	IC1/2/3 Chemotherapy Subset 3
Subject analysis set type	Sub-group analysis

Subject analysis set description:

PD-L1 immunohistochemistry (IHC) score of IC1/2/3 analyzed for Duration of Response. DOR analyses was performed on the subset of subjects who achieved an objective response.

Subject analysis set title	IC1/2/3 Atezolizumab Subset 3
Subject analysis set type	Sub-group analysis

Subject analysis set description:

PD-L1 immunohistochemistry (IHC) score of IC1/2/3 analyzed for Duration of Response. DOR analyses was performed on the subset of subjects who achieved an objective response.

Subject analysis set title	IC2/3 Chemotherapy Subset 4
Subject analysis set type	Sub-group analysis

Subject analysis set description:

PD-L1 immunohistochemistry (IHC) score of IC2/3 analyzed for Adverse Events. Safety analyses was performed on all randomized subjects who received any amount of study treatment, with subjects grouped according to whether any amount of atezolizumab was received including the case when atezolizumab was received in error.

Subject analysis set title	IC2/3 Atezolizumab Subset 4
Subject analysis set type	Sub-group analysis

Subject analysis set description:

PD-L1 immunohistochemistry (IHC) score of IC2/3 analyzed for Adverse Events. Safety analyses was performed on all randomized subjects who received any amount of study treatment, with subjects grouped according to whether any amount of atezolizumab was received including the case when atezolizumab was received in error.

Subject analysis set title	IC1/2/3 Chemotherapy Subset 4
Subject analysis set type	Sub-group analysis

Subject analysis set description:

PD-L1 immunohistochemistry (IHC) score of IC1/2/3 analyzed for Adverse Events. Safety analyses was performed on all randomized subjects who received any amount of study treatment, with subjects grouped according to whether any amount of atezolizumab was received including the case when atezolizumab was received in error.

Subject analysis set title	IC1/2/3 Atezolizumab Subset 5
Subject analysis set type	Sub-group analysis

Subject analysis set description:

ATA evaluable population, defined as patients who received atezolizumab treatment and had at least one post-treatment ATA result, with PD-L1 immunohistochemistry (IHC) score of IC1/2/3

Subject analysis set title	IC2/3 Atezolizumab Subset 5
Subject analysis set type	Sub-group analysis

Subject analysis set description:

ATA evaluable population, defined as subjects who received atezolizumab treatment and had at least one post-treatment ATA result, with PD-L1 immunohistochemistry (IHC) score of IC2/3.

Primary: Overall Survival (OS)	
End point title	Overall Survival (OS)
End point description:	
OS was defined as time from randomization to death from any cause.	
End point type	Primary
End point timeframe:	
Between randomization and death due to any cause, up to approximately 25 months after first participant enrolled	

End point values	Chemotherapy (Vinflunine, Paclitaxel, or Docetaxel)	Atezolizumab	IC2/3 Chemotherapy Subset 1	IC2/3 Atezolizumab Subset 1
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	464	467	118	116
Units: Months				
median (confidence interval 95%)	8.0 (7.2 to 8.6)	8.6 (7.8 to 9.6)	10.6 (8.4 to 12.2)	11.1 (8.6 to 15.5)

End point values	IC1/2/3 Chemotherapy Subset 1	IC1/2/3 Atezolizumab Subset 1		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	309	316		
Units: Months				
median (confidence interval 95%)	8.2 (7.4 to 9.5)	8.9 (8.2 to 10.9)		

Statistical analyses

Statistical analysis title	Overall Survival
Comparison groups	Chemotherapy (Vinflunine, Paclitaxel, or Docetaxel) v Atezolizumab
Number of subjects included in analysis	931
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0378
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	0.99

Statistical analysis title	Overall Survival
Comparison groups	IC2/3 Chemotherapy Subset 1 v IC2/3 Atezolizumab Subset 1
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4134
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	1.21

Statistical analysis title	Overall Survival
Comparison groups	IC1/2/3 Chemotherapy Subset 1 v IC1/2/3 Atezolizumab Subset 1
Number of subjects included in analysis	625
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1392
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.05

Secondary: Percentage of Participants With Objective Response Rate (ORR) as Determined by the Investigator With Use of Response Evaluation Criteria In Solid Tumors Version 1.1 (RECIST v1.1)

End point title	Percentage of Participants With Objective Response Rate (ORR) as Determined by the Investigator With Use of Response Evaluation Criteria In Solid Tumors Version 1.1 (RECIST v1.1)

End point description:

ORR was defined as the percentage of participants who had an objective response. Objective response was defined as either a complete response (CR) or partial response (PR) as determined by the investigator with use of Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1). Objective response in this study did not need to be a confirmed response. CR: disappearance of all target lesions. PR: At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR. ORR=CR+PR

End point type	Secondary

End point timeframe:

Up to approximately 25 months after first participant enrolled

End point values	Chemotherapy (Vinflunine, Paclitaxel, or Docetaxel)	Atezolizumab	IC2/3 Chemotherapy Subset 2	IC2/3 Atezolizumab Subset 2
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	461	462	116	113
Units: Percentage of participants				
number (confidence interval 95%)	20.8 (17.21 to 24.82)	15.4 (12.20 to 18.99)	29.3 (21.23 to 38.48)	26.5 (18.68 to 35.68)

End point values	IC1/2/3 Chemotherapy Subset 2	IC1/2/3 Atezolizumab Subset 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	306	312		
Units: Percentage of participants				
number (confidence interval 95%)	22.2 (17.69 to 27.30)	16.3 (12.42 to 20.93)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS) as Determined by the Investigator With Use of RECIST v1.1

End point title	Progression-free Survival (PFS) as Determined by the Investigator With Use of RECIST v1.1

End point description:

PFS was defined as the time between the date of randomization and the date of first documented progression of disease (PD) or death, whichever occurred first. PD was determined on the basis of investigator assessment with use of RECIST v1.1. PD: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline). In addition to the relative increase of 20%, the sum of diameters had to demonstrate an absolute increase of >/= 5 millimeters (mm).

End point type	Secondary

End point timeframe:

Up to approximately 25 months after first participant enrolled

End point values	Chemotherapy (Vinflunine, Paclitaxel, or Docetaxel)	Atezolizumab	IC2/3 Chemotherapy Subset 1	IC2/3 Atezolizumab Subset 1
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	464	467	118	116
Units: months				
median (confidence interval 95%)	4.0 (3.4 to 4.2)	2.1 (2.1 to 2.2)	4.2 (3.7 to 5.0)	2.4 (2.1 to 4.2)

End point values	IC1/2/3 Chemotherapy Subset 1	IC1/2/3 Atezolizumab Subset 1		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	309	316		
Units: months				
median (confidence interval 95%)	4.1 (3.6 to 4.2)	2.1 (2.1 to 2.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) as Determined by the Investigator With Use of RECIST v1.1

End point title	Duration of Response (DOR) as Determined by the Investigator With Use of RECIST v1.1

End point description:

DOR was defined as the time from first occurrence of a CR or PR, whichever came first, to first documented PD or death, whichever occurred first. PD was determined on the basis of investigator assessment with use of RECIST v1.1. CR: disappearance of all target lesions. PR: At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR. PD: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline). In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of >/= 5 mm. Note: 999999 = The DOR data was not mature at the time of clinical cutoff (i.e., majority of the responders are still ongoing), so the upper confidence interval was not estimable.

End point type	Secondary

End point timeframe:

Up to approximately 25 months after first participant enrolled

End point values	Chemotherapy (Vinflunine, Paclitaxel, or Docetaxel)	Atezolizumab	IC2/3 Chemotherapy Subset 3	IC2/3 Atezolizumab Subset 3
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	96	71	34	30
Units: months				
median (confidence interval 95%)	5.3 (4.2 to 6.3)	21.7 (9.9 to 21.7)	6.4 (4.2 to 8.3)	13.0 (6.6 to 999999)

End point values	IC1/2/3 Chemotherapy Subset 3	IC1/2/3 Atezolizumab Subset 3		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	68	51		
Units: months				
median (confidence interval 95%)	5.5 (4.2 to 7.4)	13.0 (6.9 to 999999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Adverse Events (AEs)

End point title	Percentage of Participants With Adverse Events (AEs)

End point description:

An adverse event is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as adverse events.

End point type	Secondary

End point timeframe:

Up to approximately 25 months after first participant enrolled

End point values	Chemotherapy (Vinflunine, Paclitaxel, or Docetaxel)	Atezolizumab	IC1/2/3 Atezolizumab Subset 2	IC2/3 Chemotherapy Subset 4
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	443	459	312	112
Units: percentage				
number (not applicable)	98.2	95.4	96.8	98.2

End point values	IC2/3 Atezolizumab Subset 4	IC1/2/3 Chemotherapy Subset 4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	114	297		
Units: percentage				
number (not applicable)	97.4	98.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Anti-therapeutic Antibodies (ATA) to Atezolizumab

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

End point description:

Subjects were considered post-baseline ATA positive if they had post-baseline ATAs to Atezolizumab that were treatment-induced or treatment-enhanced. Subjects had treatment-induced ATAs if they had a baseline-negative ATA result and developed ATAs at any time after initial drug administration. Subjects had treatment-enhanced ATAs if they had a baseline-positive ATA result that showed an enhanced signal that was >/= 0.60 titer units at any time after initial drug initiation.

End point type	Secondary

End point timeframe:

Predose (0 hours) on Day 1 of Cycles 1, 2, 3, 4 and every 8 cycles thereafter; at treatment discontinuation (up to 25 months); at 120 days after last dose of atezolizumab (up to 25 months; each cycle is 21 days)

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 analyses for this end point.

End point values	Atezolizumab	IC1/2/3 Atezolizumab Subset 5	IC2/3 Atezolizumab Subset 5	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	427	289	106	
Units: percentage of participants				
number (not applicable)	33.3	33.0	35.0	

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:

Cmax was measured for all subjects that received at least one dose of Atezolizumab.

End point type	Secondary

End point timeframe:

30 minutes post dose on Day 1 of Cycles 1

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 analyses for this end point.

End point values	Atezolizumab			
Subject group type	Reporting group			
Number of subjects analysed	467			
Units: mcg/mL				
geometric mean (standard deviation)	334 (± 125)			

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:

Cmin was measured for all subjects that received at least one dose of Atezolizumab.

End point type	Secondary

End point timeframe:

Predose (0 hours) on Day 1 of Cycles 1, 2, 3, 4 and every 8 cycles thereafter; at treatment discontinuation (up to 25 months); at 120 days after last dose of atezolizumab (up to 25 months; each cycle is 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 analyses for this end point.

End point values	Atezolizumab			
Subject group type	Reporting group			
Number of subjects analysed	467			
Units: mcg/mL				
geometric mean (standard deviation)				
Cycle 2, day 1|	67.5 (± 29.1)			
Cycle 3, day 1|	95.1 (± 46.5)			
Cycle 4, day 1|	122 (± 56.9)			
Cycle 8, day 1|	159 (± 72.4)			
Cycle 16, day 1|	190 (± 94.7)			
Cycle 24, day 1|	190 (± 98.7)			
Cycle 32, day 1|	223 (± 87.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organisation for Research and

Treatment of Cancer (EORTC) Quality-of-Life Questionnaire Core 30 (QLQ-C30) Score: Global Health Status Scale

End point title	Change From Baseline in European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire Core 30 (QLQ-C30) Score: Global Health Status Scale

End point description:

The EORTC QLQ-C30 includes five functional scales (physical, role, cognitive, emotional, social); a global health status (GHS)/quality of life (QoL) scale; and items measuring fatigue, pain, nausea and vomiting, dyspnea, appetite loss, sleep disturbance, constipation, diarrhea, and financial difficulties. The score range for each scale and single-item measure is 0 to 100, where higher scores indicate a higher response level (i.e., better functioning, better QoL, worse symptoms). Key scales included physical functioning, and fatigue, and GHS.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 (prior to any health care interaction), on Day 1 of each subsequent cycle, and at 30 days after the last treatment dose (Up to approximately 25 months; each cycle is 21 days)

End point values	Chemotherapy (Vinflunine, Paclitaxel, or Docetaxel)	Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	381	408		
Units: Participants				
arithmetic mean (standard deviation)				
Baseline (Cycle 1, Day 1)	61.49 (± 22.30)	64.19 (± 21.72)		
Change from baseline: Cycle 2, Day 1	-5.47 (± 20.02)	-6.18 (± 20.07)		
Change from baseline: Cycle 3, Day 1	-3.76 (± 22.34)	-4.67 (± 20.89)		
Change from baseline: Cycle 4, Day 1	-1.48 (± 19.71)	-0.53 (± 20.23)		
Change from baseline: Cycle 12, Day 1	-3.95 (± 24.33)	-0.56 (± 22.31)		
Change from baseline: Cycle 20, Day 1	-2.27 (± 16.28)	1.10 (± 21.88)		
Change from baseline: Cycle 28, Day 1	-11.67 (± 7.45)	-5.26 (± 33.82)		
Change from baseline:Treatment Discont. Visit	-10.77 (± 24.15)	-16.71 (± 24.39)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire Core 30 (QLQ-C30) Score: Physical Functioning Scale

End point title	Change From Baseline in European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire Core 30 (QLQ-C30) Score: Physical Functioning Scale

End point description:

The EORTC QLQ-C30 includes five functional scales (physical, role, cognitive, emotional, social); a global health status (GHS)/quality of life (QoL) scale; and items measuring fatigue, pain, nausea and vomiting, dyspnea, appetite loss, sleep disturbance, constipation, diarrhea, and financial difficulties. The score range for each scale and single-item measure is 0 to 100, where higher scores indicate a higher response level (i.e., better functioning, better QoL, worse symptoms). Key scales included physical functioning, and fatigue, and GHS.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 (prior to any health care interaction), on Day 1 of each subsequent cycle, and at 30 days after the last treatment dose (Up to approximately 25 months; each cycle is 21 days)

End point values	Chemotherapy (Vinflunine, Paclitaxel, or Docetaxel)	Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	381	408		
Units: Participants				
arithmetic mean (standard deviation)				
Baseline (Cycle 1, Day 1)|	74.23 (± 22.55)	76.37 (± 19.66)		
Change from baseline: Cycle 2, Day 1|	-4.80 (± 15.70)	-7.56 (± 18.24)		
Change from baseline: Cycle 3, Day 1|	-5.64 (± 17.37)	-7.06 (± 19.62)		
Change from baseline: Cycle 4, Day 1|	-4.41 (± 16.25)	-3.81 (± 17.49)		
Change from baseline: Cycle 12, Day 1|	-6.97 (± 20.20)	0.89 (± 16.23)		
Change from baseline: Cycle 20, Day 1|	-3.03 (± 11.30)	3.48 (± 13.56)		
Change from baseline: Cycle 28, Day 1|	-18.67 (± 24.68)	3.51 (± 20.53)		
Change from baseline: Treatment Discont. Visit|	-15.58 (± 25.67)	-20.19 (± 25.52)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire Core 30 (QLQ-C30) Score: Fatigue Symptom Scale

End point title	Change From Baseline in European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire Core 30 (QLQ-C30) Score: Fatigue Symptom Scale

End point description:

The EORTC QLQ-C30 includes five functional scales (physical, role, cognitive, emotional, social); a global health status (GHS)/quality of life (QoL) scale; and items measuring fatigue, pain, nausea and vomiting, dyspnea, appetite loss, sleep disturbance, constipation, diarrhea, and financial difficulties. The score range for each scale and single-item measure is 0 to 100, where higher scores indicate a higher response level (i.e., better functioning, better QoL, worse symptoms). Key scales included physical functioning, and fatigue, and GHS.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 (prior to any health care interaction), on Day 1 of each subsequent cycle, and at 30 days after the last treatment dose (Up to approximately 25 months; each cycle is 21 days)

End point values	Chemotherapy (Vinflunine, Paclitaxel, or Docetaxel)	Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	381	408		
Units: Participants				
arithmetic mean (standard deviation)				
Fatigue Symptom: Baseline (Cycle 1, Day 1)|	34.67 (± 26.66)	32.87 (± 23.88)		
Change from baseline: Cycle 2, Day 1|	10.71 (± 23.13)	10.56 (± 21.82)		
Change from baseline: Cycle 3, Day 1|	11.04 (± 25.48)	9.41 (± 24.80)		
Change from baseline: Cycle 4, Day 1|	7.48 (± 22.63)	3.67 (± 23.57)		
Change from baseline: Cycle 12, Day 1|	5.70 (± 27.44)	-0.95 (± 23.27)		
Change from baseline: Cycle 20, Day 1|	11.11 (± 28.97)	-8.05 (± 21.97)		
Change from baseline: Cycle 28, Day 1|	15.56 (± 16.85)	-12.28 (± 28.42)		
Change from baseline: Treatment Discont. Visit|	17.27 (± 28.15)	19.60 (± 25.95)		

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: 13 March 2017 (up to 25 months)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Atezolizumab

Reporting group description:

Atezolizumab was administered intravenously at a fixed dose of 1200 milligrams (mg) on Day 1 of each 21-day cycle. Participants received atezolizumab as long as they continue to experience clinical benefit in the opinion of the investigator until unacceptable toxicity or symptomatic deterioration attributed to disease progression as determined by the investigator

Reporting group title	Chemotherapy (Vinflunine, Paclitaxel, or Docetaxel)

Reporting group description:

Participants randomized to the chemotherapy arm will receive vinflunine, paclitaxel, or docetaxel per the investigator's choice. Vinflunine 320 milligrams per square meter (mg/m^2), paclitaxel 175 mg/m^2, or docetaxel 75 mg/m^2 will be administered intravenously on Day 1 of each 21-day cycle until disease progression per standard RECIST v1.1 or unacceptable toxicity.

Serious adverse events	Atezolizumab	Chemotherapy (Vinflunine, Paclitaxel, or Docetaxel)	
Total subjects affected by serious adverse events			
subjects affected / exposed	188 / 459 (40.96%)	191 / 443 (43.12%)	
number of deaths (all causes)	318	343	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon Cancer			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mantle Cell Lymphoma			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm Malignant			

subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumor Associated Fever			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep Vein Thrombosis			
subjects affected / exposed	4 / 459 (0.87%)	2 / 443 (0.45%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	2 / 459 (0.44%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypertension			
subjects affected / exposed	0 / 459 (0.00%)	2 / 443 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 459 (0.00%)	3 / 443 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Abdominal Cavity Drainage			
subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebroplasty			

subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	3 / 459 (0.65%)	3 / 443 (0.68%)	
occurrences causally related to treatment / all	0 / 3	2 / 3	
deaths causally related to treatment / all	0 / 3	2 / 3	
Fatigue			
subjects affected / exposed	5 / 459 (1.09%)	5 / 443 (1.13%)	
occurrences causally related to treatment / all	1 / 5	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
General Physical Health Deterioration			
subjects affected / exposed	2 / 459 (0.44%)	4 / 443 (0.90%)	
occurrences causally related to treatment / all	1 / 2	1 / 4	
deaths causally related to treatment / all	1 / 1	0 / 0	
Influenza Like Illness			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection Site Reaction			
subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 459 (0.22%)	2 / 443 (0.45%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple Organ Dysfunction Syndrome			
subjects affected / exposed	0 / 459 (0.00%)	2 / 443 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Non-Cardiac Chest Pain			

subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction			
subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema Peripheral			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	3 / 459 (0.65%)	5 / 443 (1.13%)	
occurrences causally related to treatment / all	0 / 3	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Swelling			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	16 / 459 (3.49%)	6 / 443 (1.35%)	
occurrences causally related to treatment / all	6 / 17	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Strangulated Hernia			
subjects affected / exposed	1 / 459 (0.22%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug Hypersensitivity			

subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Vaginal Haemorrhage			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	7 / 459 (1.53%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	5 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Effusion			
subjects affected / exposed	2 / 459 (0.44%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Aspiration			
subjects affected / exposed	1 / 459 (0.22%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	4 / 459 (0.87%)	2 / 443 (0.45%)	
occurrences causally related to treatment / all	3 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumothorax			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Productive Cough			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Embolism			
subjects affected / exposed	3 / 459 (0.65%)	2 / 443 (0.45%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Distress			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Failure			
subjects affected / exposed	2 / 459 (0.44%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Psychiatric disorders			
Completed Suicide			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Confusional State			
subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device Dislocation			
subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device Occlusion			
subjects affected / exposed	1 / 459 (0.22%)	3 / 443 (0.68%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	2 / 459 (0.44%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate Aminotransferase Increased			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood Bilirubin Increased			
subjects affected / exposed	1 / 459 (0.22%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood Calcium Increased			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood Creatinine Increased			
subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver Function Test Abnormal			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil Count Decreased			
subjects affected / exposed	0 / 459 (0.00%)	5 / 443 (1.13%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet Count Decreased			
subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Transaminases Increased			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White Blood Cell Count Decreased			
subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Compression Fracture			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral Neck Fracture			
subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
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	2 / 459 (0.44%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Limb Fracture			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar Vertebral Fracture			
subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Compression Fracture			
subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Stoma Site Haemorrhage			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to Various Agents			
subjects affected / exposed	1 / 459 (0.22%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urostomy Complication			
subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute Coronary Syndrome			
subjects affected / exposed	0 / 459 (0.00%)	2 / 443 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Myocardial Infarction			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina Pectoris			
subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Fibrillation			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular Block			
subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Arrest			

subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardio-Respiratory Arrest			
subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Myocardial Infarction			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial Effusion			
subjects affected / exposed	2 / 459 (0.44%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain Oedema			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyskinesia			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			

subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
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	2 / 459 (0.44%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Leukoencephalopathy			
subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculopathy			
subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Cord Compression			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 459 (0.44%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient Ischaemic Attack			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (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			
Anemia			

subjects affected / exposed	8 / 459 (1.74%)	5 / 443 (1.13%)	
occurrences causally related to treatment / all	3 / 8	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone Marrow Failure			
subjects affected / exposed	0 / 459 (0.00%)	2 / 443 (0.45%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile Neutropenia			
subjects affected / exposed	1 / 459 (0.22%)	22 / 443 (4.97%)	
occurrences causally related to treatment / all	1 / 1	23 / 25	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 459 (0.00%)	13 / 443 (2.93%)	
occurrences causally related to treatment / all	0 / 0	14 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	2 / 459 (0.44%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 459 (0.22%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Macular Fibrosis			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papilloedema			

subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual Impairment			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	4 / 459 (0.87%)	9 / 443 (2.03%)	
occurrences causally related to treatment / all	0 / 4	7 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Pain Lower			
subjects affected / exposed	3 / 459 (0.65%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal Haemorrhage			
subjects affected / exposed	2 / 459 (0.44%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune Colitis			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	3 / 459 (0.65%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis Ulcerative			

subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 459 (0.44%)	20 / 443 (4.51%)	
occurrences causally related to treatment / all	0 / 2	21 / 23	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	6 / 459 (1.31%)	3 / 443 (0.68%)	
occurrences causally related to treatment / all	5 / 6	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal Obstruction			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	2 / 459 (0.44%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eterocolitis			
subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eterovesical Fistula			
subjects affected / exposed	1 / 459 (0.22%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Functional Gastrointestinal Disorder			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric Haemorrhage			

subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Haemorrhage			
subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal Perforation			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 459 (0.22%)	6 / 443 (1.35%)	
occurrences causally related to treatment / all	0 / 2	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal Hernia			
subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal Obstruction			
subjects affected / exposed	2 / 459 (0.44%)	2 / 443 (0.45%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal Perforation			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Jejunal Perforation			
subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Large Intestinal Obstruction			

subjects affected / exposed	2 / 459 (0.44%)	2 / 443 (0.45%)	
occurrences causally related to treatment / all	0 / 2	2 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nausea			
subjects affected / exposed	1 / 459 (0.22%)	4 / 443 (0.90%)	
occurrences causally related to treatment / all	1 / 1	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	3 / 459 (0.65%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal Haemorrhage			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (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	1 / 459 (0.22%)	4 / 443 (0.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	2 / 459 (0.44%)	4 / 443 (0.90%)	
occurrences causally related to treatment / all	1 / 3	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	3 / 459 (0.65%)	2 / 443 (0.45%)	
occurrences causally related to treatment / all	1 / 4	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Autoimmune Hepatitis			
subjects affected / exposed	2 / 459 (0.44%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile Duct Obstruction			

subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary Dilation			
subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular Injury			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal Vein Thrombosis			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Psoriasis			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic Epidermal Necrolysis			

subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	11 / 459 (2.40%)	6 / 443 (1.35%)	
occurrences causally related to treatment / all	0 / 12	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anuria			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder Perforation			
subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder Tamponade			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	9 / 459 (1.96%)	7 / 443 (1.58%)	
occurrences causally related to treatment / all	1 / 18	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	2 / 459 (0.44%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postrenal Failure			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Failure			

subjects affected / exposed	3 / 459 (0.65%)	4 / 443 (0.90%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Haematoma			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral Haemorrhage			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Bladder Haemorrhage			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Retention			
subjects affected / exposed	6 / 459 (1.31%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	1 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary Tract Obstruction			
subjects affected / exposed	1 / 459 (0.22%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Pain			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinoma			
subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism			

subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothyroidism			
subjects affected / exposed	2 / 459 (0.44%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 459 (0.22%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back Pain			
subjects affected / exposed	6 / 459 (1.31%)	4 / 443 (0.90%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone Pain			
subjects affected / exposed	1 / 459 (0.22%)	3 / 443 (0.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin Pain			
subjects affected / exposed	2 / 459 (0.44%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in Extremity			

subjects affected / exposed	1 / 459 (0.22%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological Fracture			
subjects affected / exposed	0 / 459 (0.00%)	3 / 443 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Arthritis			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Arthritis Infective			
subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
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 / 459 (0.00%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial Infection			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			

subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device Related Infection			
subjects affected / exposed	2 / 459 (0.44%)	3 / 443 (0.68%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal Infection			
subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal Sepsis			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia Infection			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia Pyelonephritis			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia Sepsis			
subjects affected / exposed	1 / 459 (0.22%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
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 / 459 (0.22%)	4 / 443 (0.90%)	
occurrences causally related to treatment / all	1 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney Infection			
subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella Infection			
subjects affected / exposed	2 / 459 (0.44%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Respiratory Tract Infection			
subjects affected / exposed	2 / 459 (0.44%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Infection			
subjects affected / exposed	2 / 459 (0.44%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningoencephalitis Viral			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic Infection			
subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic Sepsis			

subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ophthalmic Herpes Zoster			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	5 / 459 (1.09%)	6 / 443 (1.35%)	
occurrences causally related to treatment / all	0 / 6	3 / 6	
deaths causally related to treatment / all	0 / 1	2 / 3	
Pyelonephritis			
subjects affected / exposed	2 / 459 (0.44%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Tract Infection			
subjects affected / exposed	2 / 459 (0.44%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sepsis			
subjects affected / exposed	7 / 459 (1.53%)	14 / 443 (3.16%)	
occurrences causally related to treatment / all	0 / 7	7 / 15	
deaths causally related to treatment / all	0 / 1	1 / 4	
Septic Shock			
subjects affected / exposed	2 / 459 (0.44%)	3 / 443 (0.68%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 1	1 / 1	
Spinal Cord Infection			

subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal Infection			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic Shock Syndrome			
subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Urinary Tract Infection			
subjects affected / exposed	21 / 459 (4.58%)	14 / 443 (3.16%)	
occurrences causally related to treatment / all	0 / 24	1 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection Bacterial			
subjects affected / exposed	0 / 459 (0.00%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 459 (0.22%)	11 / 443 (2.48%)	
occurrences causally related to treatment / all	0 / 1	5 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	2 / 459 (0.44%)	3 / 443 (0.68%)	
occurrences causally related to treatment / all	1 / 2	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes Mellitus			

subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic Ketoacidosis			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to Thrive			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypercalcaemia			
subjects affected / exposed	3 / 459 (0.65%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 459 (0.22%)	0 / 443 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 459 (0.22%)	1 / 443 (0.23%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	4 / 459 (0.87%)	3 / 443 (0.68%)	
occurrences causally related to treatment / all	2 / 4	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Atezolizumab	Chemotherapy (Vinflunine, Paclitaxel, or Docetaxel)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	408 / 459 (88.89%)	416 / 443 (93.91%)	
Investigations			
Blood Creatinine Increased			
subjects affected / exposed	35 / 459 (7.63%)	11 / 443 (2.48%)	
occurrences (all)	37	12	
Neutrophil Count Decreased			
subjects affected / exposed	0 / 459 (0.00%)	25 / 443 (5.64%)	
occurrences (all)	0	48	
Weight Decreased			
subjects affected / exposed	44 / 459 (9.59%)	45 / 443 (10.16%)	
occurrences (all)	44	46	
Nervous system disorders			
Dizziness			
subjects affected / exposed	25 / 459 (5.45%)	30 / 443 (6.77%)	
occurrences (all)	25	32	
Dysgeusia			
subjects affected / exposed	11 / 459 (2.40%)	25 / 443 (5.64%)	
occurrences (all)	13	27	
Headache			
subjects affected / exposed	34 / 459 (7.41%)	26 / 443 (5.87%)	
occurrences (all)	39	35	
Neuropathy Peripheral			
subjects affected / exposed	7 / 459 (1.53%)	53 / 443 (11.96%)	
occurrences (all)	8	63	
Paraesthesia			
subjects affected / exposed	16 / 459 (3.49%)	29 / 443 (6.55%)	
occurrences (all)	16	32	
Peripheral Sensory Neuropathy			
subjects affected / exposed	5 / 459 (1.09%)	41 / 443 (9.26%)	
occurrences (all)	6	43	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	88 / 459 (19.17%)	123 / 443 (27.77%)	
occurrences (all)	92	141	
Neutropenia			
subjects affected / exposed	4 / 459 (0.87%)	55 / 443 (12.42%)	
occurrences (all)	4	72	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	88 / 459 (19.17%)	105 / 443 (23.70%)	
occurrences (all)	100	140	
Fatigue			
subjects affected / exposed	124 / 459 (27.02%)	137 / 443 (30.93%)	
occurrences (all)	144	163	
Mucosal Inflammation			
subjects affected / exposed	24 / 459 (5.23%)	47 / 443 (10.61%)	
occurrences (all)	27	64	
Oedema Peripheral			
subjects affected / exposed	48 / 459 (10.46%)	36 / 443 (8.13%)	
occurrences (all)	54	41	
Pain			
subjects affected / exposed	24 / 459 (5.23%)	33 / 443 (7.45%)	
occurrences (all)	25	36	
Pyrexia			
subjects affected / exposed	86 / 459 (18.74%)	63 / 443 (14.22%)	
occurrences (all)	117	76	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	49 / 459 (10.68%)	58 / 443 (13.09%)	
occurrences (all)	56	63	
Abdominal Pain Upper			
subjects affected / exposed	23 / 459 (5.01%)	27 / 443 (6.09%)	
occurrences (all)	23	32	
Constipation			
subjects affected / exposed	121 / 459 (26.36%)	162 / 443 (36.57%)	
occurrences (all)	135	219	
Diarrhoea			

subjects affected / exposed	90 / 459 (19.61%)	94 / 443 (21.22%)	
occurrences (all)	122	115	
Dry Mouth			
subjects affected / exposed	28 / 459 (6.10%)	8 / 443 (1.81%)	
occurrences (all)	33	8	
Nausea			
subjects affected / exposed	99 / 459 (21.57%)	136 / 443 (30.70%)	
occurrences (all)	115	170	
Stomatitis			
subjects affected / exposed	13 / 459 (2.83%)	35 / 443 (7.90%)	
occurrences (all)	15	41	
Vomiting			
subjects affected / exposed	52 / 459 (11.33%)	79 / 443 (17.83%)	
occurrences (all)	63	106	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	55 / 459 (11.98%)	30 / 443 (6.77%)	
occurrences (all)	58	33	
Dyspnoea			
subjects affected / exposed	59 / 459 (12.85%)	43 / 443 (9.71%)	
occurrences (all)	64	47	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 459 (0.00%)	124 / 443 (27.99%)	
occurrences (all)	0	126	
Pruritus			
subjects affected / exposed	63 / 459 (13.73%)	19 / 443 (4.29%)	
occurrences (all)	78	26	
Rash			
subjects affected / exposed	52 / 459 (11.33%)	28 / 443 (6.32%)	
occurrences (all)	60	37	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	24 / 459 (5.23%)	25 / 443 (5.64%)	
occurrences (all)	24	25	
Insomnia			

subjects affected / exposed	42 / 459 (9.15%)	41 / 443 (9.26%)	
occurrences (all)	44	41	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	44 / 459 (9.59%)	26 / 443 (5.87%)	
occurrences (all)	56	29	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	48 / 459 (10.46%)	60 / 443 (13.54%)	
occurrences (all)	62	80	
Back Pain			
subjects affected / exposed	80 / 459 (17.43%)	51 / 443 (11.51%)	
occurrences (all)	90	53	
Bone Pain			
subjects affected / exposed	22 / 459 (4.79%)	24 / 443 (5.42%)	
occurrences (all)	25	28	
Myalgia			
subjects affected / exposed	25 / 459 (5.45%)	55 / 443 (12.42%)	
occurrences (all)	27	68	
Pain in Extremity			
subjects affected / exposed	37 / 459 (8.06%)	47 / 443 (10.61%)	
occurrences (all)	46	54	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	26 / 459 (5.66%)	11 / 443 (2.48%)	
occurrences (all)	36	13	
Urinary Tract Infection			
subjects affected / exposed	79 / 459 (17.21%)	56 / 443 (12.64%)	
occurrences (all)	118	73	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	131 / 459 (28.54%)	110 / 443 (24.83%)	
occurrences (all)	141	133	
Hypokalaemia			
subjects affected / exposed	15 / 459 (3.27%)	23 / 443 (5.19%)	
occurrences (all)	16	26	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 September 2015	Protocol was amended to include changing the ratio of patients treated with vinflunine versus taxane such that it will be possible to conduct a subgroup analysis of patients treated with vinflunine versus atezolizumab. Within the control arm of the study, to allow more patients intended to receive vinflunine treatment when randomized into this trial, the maximum percentage of the patients who are treated with a taxane (paclitaxel or docetaxel) will be decreased from 50% to 40% with implementation of a cap. Once enrollment has reached 40% within the taxane intent-to-treat population, subsequent patients randomized to the control arm will receive vinflunine treatment.
08 March 2016	Protocol was amended to include an update to the use of any live vaccine to be prohibited 28 days prior to randomization.
21 June 2016	Protocol was amended to include an increase in the total number of patients enrolled in the study from 767 to 931 to achieve the pre-specified minimum number of 230 IC2/3 patients and 537 IC1/2/3 patients. Subsequently, the numbers of events were revised to ensure the study retains sufficient power and follow-up to estimate overall survival (OS).
28 October 2016	Protocol was amended based on updated clinical data regarding the atezolizumab half-life of 27 days, the following changes have been implemented: The period during which female patients must remain abstinent or use contraception and the length of follow-up of pregnancy reporting has been revised from 90 days to 5 months after the last dose of atezolizumab;The period during which patients must agree not to receive live, attenuated vaccine has been revised from 90 days to 5 months after the last dose of atezolizumab.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported