Clinical trial results:
A Phase II, Multicenter, Single-Arm Study OF Atezolizumab In Patients With PD-L1-Positive Locally Advanced Or Metastatic Non-Small Cell Lung Cancer

Summary

EudraCT number	2013-003330-32
Trial protocol	SI IT BE DE GB NL FR ES BG
Global end of trial date	11 January 2019

Results information

Result version number	v2 (current)
This version publication date	18 December 2019
First version publication date	01 July 2016
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	GO28754

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02031458
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	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, 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	Final
Date of interim/final analysis	11 January 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective for this study is to evaluate the efficacy of atezolizumab in participants with programmed cell death−1 ligand 1 (PD-L1)−positive locally advanced or metastatic non−small cell lung cancer (NSCLC), as measured by: Independent review facility (IRF)-assessed objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (v1.1) .

Protection of trial subjects:

All study subjects were required to read and sign and Informed Consent Form. The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 January 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 21
Country: Number of subjects enrolled	Hong Kong: 6
Country: Number of subjects enrolled	Japan: 27
Country: Number of subjects enrolled	Singapore: 18
Country: Number of subjects enrolled	Bosnia and Herzegovina: 8
Country: Number of subjects enrolled	Switzerland: 41
Country: Number of subjects enrolled	Georgia: 20
Country: Number of subjects enrolled	Turkey: 18
Country: Number of subjects enrolled	Canada: 47
Country: Number of subjects enrolled	United States: 217
Country: Number of subjects enrolled	Netherlands: 28
Country: Number of subjects enrolled	Slovenia: 8
Country: Number of subjects enrolled	Spain: 48
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	Belgium: 20
Country: Number of subjects enrolled	Bulgaria: 4
Country: Number of subjects enrolled	France: 64
Country: Number of subjects enrolled	Germany: 29
Country: Number of subjects enrolled	Italy: 24

Worldwide total number of subjects	659
EEA total number of subjects	236

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)	331
From 65 to 84 years	323
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

Since the primary cut-off date May 8, 2015 one participant in Cohort 1 has moved to Cohort 2 and one participant in Cohort 3 was moved to Cohort 2.

Pre-assignment

Screening details:

Screening was performed from Day -28 to Day -1.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1: First Line Atezolizumab

Arm description:

Participants received 1200 milligrams (mg) atezolizumab every 3 weeks (Day 1 of 21 day cycle) administered by intravenous (IV) infusion until intolerable toxicity, disease progression or death. Participants in this cohort received no prior chemotherapy in locally advanced or metastatic setting.

Arm type	Experimental
Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	
Other name	Tecentriq
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1200 mg every 3 weeks

Arm title	Cohort 2: Second Line Atezolizumab

Arm description:

Participants received 1200 mg atezolizumab every 3 weeks (Day 1 of 21-day cycle) administered by IV infusion until intolerable toxicity, disease progression or death. Participants were permitted to continue treatment after progressive disease, if the following criteria were met: evidence of clinical benefit as assessed by the investigator; absence of symptoms and signs indicating unequivocal progression of disease; no decline in Eastern Cooperative Oncology Group (ECOG) performance status; absence of tumor growth at critical anatomical sites that cannot be managed by protocol-allowed medical interventions; evidence of clinical benefit as assessed by the investigator. Participants in this cohort progressed during or after prior platinum-based chemotherapy in locally advanced or metastatic setting.

Arm type	Experimental
Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	
Other name	Tecentriq
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1200 mg every 3 weeks

Arm title	Cohort 3: Third Line and Beyond Atezolizumab

Arm description:

Participants received 1200 mg atezolizumab every 3 weeks (Day 1 of 21-day cycle) administered by IV infusion until intolerable toxicity, disease progression or death. Participants were permitted to continue treatment after progressive disease, if the following criteria were met: absence of symptoms and signs

indicating unequivocal progression of disease; no decline in ECOG performance status; absence of tumor growth at critical anatomical sites that cannot be managed by protocol-allowed medical interventions; evidence of clinical benefit as assessed by the investigator. Participants in this cohort progressed during or after prior platinum-based chemotherapy and at least one additional therapy in locally advanced or metastatic setting.

Arm type	Experimental
Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	
Other name	Tecentriq
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1200 mg every 3 weeks

Number of subjects in period 1	Cohort 1: First Line Atezolizumab	Cohort 2: Second Line Atezolizumab	Cohort 3: Third Line and Beyond Atezolizumab
Started	138	269	252
Completed	0	0	0
Not completed	138	269	252
Switched over to commercial Atezolizumab	1	6	6
Physician decision	2	3	3
Consent withdrawn by subject	13	16	14
Study Terminated By Sponsor	24	42	23
Death	89	193	198
Lost to follow-up	2	5	8
Protocol deviation	7	4	-

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1: First Line Atezolizumab
Reporting group description:	
Participants received 1200 milligrams (mg) atezolizumab every 3 weeks (Day 1 of 21 day cycle) administered by intravenous (IV) infusion until intolerable toxicity, disease progression or death. Participants in this cohort received no prior chemotherapy in locally advanced or metastatic setting.	
Reporting group title	Cohort 2: Second Line Atezolizumab
Reporting group description:	
Participants received 1200 mg atezolizumab every 3 weeks (Day 1 of 21-day cycle) administered by IV infusion until intolerable toxicity, disease progression or death. Participants were permitted to continue treatment after progressive disease, if the following criteria were met: evidence of clinical benefit as assessed by the investigator; absence of symptoms and signs indicating unequivocal progression of disease; no decline in Eastern Cooperative Oncology Group (ECOG) performance status; absence of tumor growth at critical anatomical sites that cannot be managed by protocol-allowed medical interventions; evidence of clinical benefit as assessed by the investigator. Participants in this cohort progressed during or after prior platinum-based chemotherapy in locally advanced or metastatic setting.	
Reporting group title	Cohort 3: Third Line and Beyond Atezolizumab
Reporting group description:	
Participants received 1200 mg atezolizumab every 3 weeks (Day 1 of 21-day cycle) administered by IV infusion until intolerable toxicity, disease progression or death. Participants were permitted to continue treatment after progressive disease, if the following criteria were met: absence of symptoms and signs indicating unequivocal progression of disease; no decline in ECOG performance status; absence of tumor growth at critical anatomical sites that cannot be managed by protocol-allowed medical interventions; evidence of clinical benefit as assessed by the investigator. Participants in this cohort progressed during or after prior platinum-based chemotherapy and at least one additional therapy in locally advanced or metastatic setting.	

Reporting group values	Cohort 1: First Line Atezolizumab	Cohort 2: Second Line Atezolizumab	Cohort 3: Third Line and Beyond Atezolizumab
Number of subjects	138	269	252
Age categorical			
Data set "Reporting group values" is applicable from primary data cut-off May 8, 2015 to data cut-off January 11, 2019 Data set "Subject Analysis Set Values" is applicable up to primary data cut-off May 8, 2015			
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)	53	144	133
From 65-84 years	80	125	119
85 years and over	5	0	0
Age Continuous			
Data set "Reporting group values" is applicable from primary data cut-off May 8, 2015 to data cut-off January 11, 2019 Data set "Subject Analysis Set Values" is applicable up to primary data cut-off May 8, 2015			
Units: years			
median	66.8	62.4	63.6
standard deviation	± 10.3	± 10.2	± 9.4

Sex: Female, Male			
Data set "Reporting group values" is applicable from primary data cut-off May 8, 2015 to data cut-off January 11, 2019 Data set "Subject Analysis Set Values" is applicable up to primary data cut-off May 8, 2015			
Units: Subjects			
Female	68	104	100
Male	70	165	152

Reporting group values	Total		
Number of subjects	659		
Age categorical			
Data set "Reporting group values" is applicable from primary data cut-off May 8, 2015 to data cut-off January 11, 2019 Data set "Subject Analysis Set Values" is applicable up to primary data cut-off May 8, 2015			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	330		
From 65-84 years	324		
85 years and over	5		
Age Continuous			
Data set "Reporting group values" is applicable from primary data cut-off May 8, 2015 to data cut-off January 11, 2019 Data set "Subject Analysis Set Values" is applicable up to primary data cut-off May 8, 2015			
Units: years			
median			
standard deviation	-		
Sex: Female, Male			
Data set "Reporting group values" is applicable from primary data cut-off May 8, 2015 to data cut-off January 11, 2019 Data set "Subject Analysis Set Values" is applicable up to primary data cut-off May 8, 2015			
Units: Subjects			
Female	272		
Male	387		

Subject analysis sets

Subject analysis set title	Cohort 1: First Line Atezolizumab Primary Analysis
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received 1200 mg atezolizumab every 3 weeks (Day 1 of 21 day cycle) administered by IV infusion until intolerable toxicity, disease progression or death. Participants in this cohort received no prior chemotherapy in locally advanced or metastatic setting.

Subject analysis set title	Cohort 2: Second Line Atezolizumab Primary Analysis
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received 1200 mg atezolizumab every 3 weeks (Day 1 of 21-day cycle) administered by IV infusion until intolerable toxicity, disease progression or death. Participants were permitted to continue treatment after progressive disease, if the following criteria were met: evidence of clinical benefit as assessed by the investigator; absence of symptoms and signs indicating unequivocal progression of

disease; no decline in ECOG performance status; absence of tumor growth at critical anatomical sites that cannot be managed by protocol-allowed medical interventions; evidence of clinical benefit as assessed by the investigator. Participants in this cohort progressed during or after prior platinum-based chemotherapy in locally advanced or metastatic setting.

Subject analysis set title	Cohort 3: Third Line and Beyond Atezolizumab Primary Analysis
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received 1200 mg atezolizumab every 3 weeks (Day 1 of 21-day cycle) administered by IV infusion until intolerable toxicity, disease progression or death. Participants were permitted to continue treatment after progressive disease, if the following criteria were met: absence of symptoms and signs indicating unequivocal progression of disease; no decline in ECOG performance status; absence of tumor growth at critical anatomical sites that cannot be managed by protocol-allowed medical interventions; evidence of clinical benefit as assessed by the investigator. Participants in this cohort progressed during or after prior platinum-based chemotherapy and at least one additional therapy in locally advanced or metastatic setting.

Subject analysis set title	Cohorts 2 + 3
Subject analysis set type	Safety analysis

Subject analysis set description:

This sub-group included participants from cohorts 2 and 3. All participants who were treated and had evaluable pharmacokinetic samples were included in this group.

Subject analysis set title	Pharmacokinetic Evaluable Population
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received 1200 milligrams (mg) atezolizumab every 3 weeks (Day 1 of 21 day cycle) administered by intravenous (IV) infusion until intolerable toxicity, disease progression or death. All participants who were treated and had evaluable pharmacokinetic samples were included in this group.

Reporting group values	Cohort 1: First Line Atezolizumab Primary Analysis	Cohort 2: Second Line Atezolizumab Primary Analysis	Cohort 3: Third Line and Beyond Atezolizumab Primary Analysis
Number of subjects	139	267	253
Age categorical			
Data set "Reporting group values" is applicable from primary data cut-off May 8, 2015 to data cut-off January 11, 2019 Data set "Subject Analysis Set Values" is applicable up to primary data cut-off May 8, 2015			
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)	55	142	134
From 65-84 years	79	125	119
85 years and over	5	0	0
Age Continuous			
Data set "Reporting group values" is applicable from primary data cut-off May 8, 2015 to data cut-off January 11, 2019 Data set "Subject Analysis Set Values" is applicable up to primary data cut-off May 8, 2015			
Units: years			
median	66.7	62.4	63.6
standard deviation	± 10.4	± 10.2	± 9.4
Sex: Female, Male			
Data set "Reporting group values" is applicable from primary data cut-off May 8, 2015 to data cut-off January 11, 2019 Data set "Subject Analysis Set Values" is applicable up to primary data cut-off May 8, 2015			

Units: Subjects			
Female	68	103	100
Male	71	164	153

Reporting group values	Cohorts 2 + 3	Pharmacokinetic Evaluable Population	
Number of subjects	520	646	
Age categorical			
Data set "Reporting group values" is applicable from primary data cut-off May 8, 2015 to data cut-off January 11, 2019 Data set "Subject Analysis Set Values" is applicable up to primary data cut-off May 8, 2015			
Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous			
Data set "Reporting group values" is applicable from primary data cut-off May 8, 2015 to data cut-off January 11, 2019 Data set "Subject Analysis Set Values" is applicable up to primary data cut-off May 8, 2015			
Units: years			
median	63		
standard deviation	± 9.3	±	
Sex: Female, Male			
Data set "Reporting group values" is applicable from primary data cut-off May 8, 2015 to data cut-off January 11, 2019 Data set "Subject Analysis Set Values" is applicable up to primary data cut-off May 8, 2015			
Units: Subjects			
Female	203		
Male	317		

End points

End points reporting groups

Reporting group title	Cohort 1: First Line Atezolizumab

Reporting group description:

Participants received 1200 milligrams (mg) atezolizumab every 3 weeks (Day 1 of 21 day cycle) administered by intravenous (IV) infusion until intolerable toxicity, disease progression or death. Participants in this cohort received no prior chemotherapy in locally advanced or metastatic setting.

Reporting group title	Cohort 2: Second Line Atezolizumab

Reporting group description:

Participants received 1200 mg atezolizumab every 3 weeks (Day 1 of 21-day cycle) administered by IV infusion until intolerable toxicity, disease progression or death. Participants were permitted to continue treatment after progressive disease, if the following criteria were met: evidence of clinical benefit as assessed by the investigator; absence of symptoms and signs indicating unequivocal progression of disease; no decline in Eastern Cooperative Oncology Group (ECOG) performance status; absence of tumor growth at critical anatomical sites that cannot be managed by protocol-allowed medical interventions; evidence of clinical benefit as assessed by the investigator. Participants in this cohort progressed during or after prior platinum-based chemotherapy in locally advanced or metastatic setting.

Reporting group title	Cohort 3: Third Line and Beyond Atezolizumab

Reporting group description:

Participants received 1200 mg atezolizumab every 3 weeks (Day 1 of 21-day cycle) administered by IV infusion until intolerable toxicity, disease progression or death. Participants were permitted to continue treatment after progressive disease, if the following criteria were met: absence of symptoms and signs indicating unequivocal progression of disease; no decline in ECOG performance status; absence of tumor growth at critical anatomical sites that cannot be managed by protocol-allowed medical interventions; evidence of clinical benefit as assessed by the investigator. Participants in this cohort progressed during or after prior platinum-based chemotherapy and at least one additional therapy in locally advanced or metastatic setting.

Subject analysis set title	Cohort 1: First Line Atezolizumab Primary Analysis
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received 1200 mg atezolizumab every 3 weeks (Day 1 of 21 day cycle) administered by IV infusion until intolerable toxicity, disease progression or death. Participants in this cohort received no prior chemotherapy in locally advanced or metastatic setting.

Subject analysis set title	Cohort 2: Second Line Atezolizumab Primary Analysis
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received 1200 mg atezolizumab every 3 weeks (Day 1 of 21-day cycle) administered by IV infusion until intolerable toxicity, disease progression or death. Participants were permitted to continue treatment after progressive disease, if the following criteria were met: evidence of clinical benefit as assessed by the investigator; absence of symptoms and signs indicating unequivocal progression of disease; no decline in ECOG performance status; absence of tumor growth at critical anatomical sites that cannot be managed by protocol-allowed medical interventions; evidence of clinical benefit as assessed by the investigator. Participants in this cohort progressed during or after prior platinum-based chemotherapy in locally advanced or metastatic setting.

Subject analysis set title	Cohort 3: Third Line and Beyond Atezolizumab Primary Analysis
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received 1200 mg atezolizumab every 3 weeks (Day 1 of 21-day cycle) administered by IV infusion until intolerable toxicity, disease progression or death. Participants were permitted to continue treatment after progressive disease, if the following criteria were met: absence of symptoms and signs indicating unequivocal progression of disease; no decline in ECOG performance status; absence of tumor growth at critical anatomical sites that cannot be managed by protocol-allowed medical interventions; evidence of clinical benefit as assessed by the investigator. Participants in this cohort progressed during or after prior platinum-based chemotherapy and at least one additional therapy in locally advanced or metastatic setting.

Subject analysis set title	Cohorts 2 + 3
Subject analysis set type	Safety analysis

Subject analysis set description:

This sub-group included participants from cohorts 2 and 3. All participants who were treated and had evaluable pharmacokinetic samples were included in this group.

Subject analysis set title	Pharmacokinetic Evaluable Population
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received 1200 milligrams (mg) atezolizumab every 3 weeks (Day 1 of 21 day cycle) administered by intravenous (IV) infusion until intolerable toxicity, disease progression or death. All participants who were treated and had evaluable pharmacokinetic samples were included in this group.

Primary: Percentage of Participants Achieving Objective Response (ORR) Per Response Evaluation Criteria In Solid Tumors (RECIST) Version (v) 1.1 as Assessed by Independent Review Facility (IRF)

End point title	Percentage of Participants Achieving Objective Response (ORR) Per Response Evaluation Criteria In Solid Tumors (RECIST) Version (v) 1.1 as Assessed by Independent Review Facility (IRF)[1]

End point description:

ORR was the percentage of participants whose confirmed best overall response was either a Partial Response (PR) or a Complete Response (CR) based upon the IRF assessment per RECIST v1.1. CR: disappearance of all target and non-target lesions. Any pathological lymph nodes (target or non-target) must have reduction in short axis to less than (<) 10 millimeters (mm); PR:greater than (>) or equal to (=) 30 percent (%) decrease from baseline in sum of diameters of target lesions, non-progressive disease (PD) non-target lesions and no new lesions. Results were reported by line of therapy and programmed death-ligand 1 (PD-L1) Expression Subgroup (tumor cell [TC]3 [TC3] or tumor-infiltrating immune cell [IC] 3 [IC3], TC3 or IC2/3, TC2/3 or IC2/3).

End point type	Primary

End point timeframe:

Screening, Every 6 weeks (± 3 days) for 12 months following Cycle 1, Day 1 and every 9 weeks (± 1 week) thereafter until disease progression, intolerable toxicity or death until data cut-off on 28 May 2015 (Up to 16 months)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analyses are attached as a chart.

End point values	Cohort 1: First Line Atezolizumab Primary Analysis	Cohort 2: Second Line Atezolizumab Primary Analysis	Cohort 3: Third Line and Beyond Atezolizumab Primary Analysis	Cohorts 2 + 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	139	267	253	520
Units: percentage of participants				
number (confidence interval 95%)				
TC3 or IC3 Responders (n= 65, 122, 115, 237)	26.2 (16.0 to 38.5)	23.8 (16.5 to 32.3)	27.0 (19.1 to 36.0)	25.35 (19.9 to 31.4)
TC3 or IC2/3 Responders (n= 123, 247, 236, 483)	21.1 (14.3 to 29.4)	17.4 (12.9 to 22.7)	18.2 (13.5 to 23.8)	17.8 (14.5 to 21.5)
TC2/3 or IC2/3 Responders (n= 139, 267, 253, 520)	19.4 (13.2 to 27.0)	17.2 (12.9 to 22.3)	17.4 (12.9 to 22.6)	17.3 (14.2 to 20.8)

Attachments (see zip file)	Statistical analysis for Objective Response/Statistical analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Objective Response Per RECIST v1.1 as Assessed by the Investigator (INV)

End point title	Percentage of Participants Achieving Objective Response Per RECIST v1.1 as Assessed by the Investigator (INV)

End point description:

ORR was the percentage of participants whose confirmed best overall response was either a PR or a CR based upon the Investigator assessment per RECIST v1.1. CR: disappearance of all target and non-target lesions. Any pathological lymph nodes (target or non-target) must have reduction in short axis to <10mm; PR: > or = 30 % decrease from baseline in sum of diameters of target lesions, non-PD non-target lesions and no new lesions. Results were reported by line of therapy (reporting arms) and PD-L1 Expression Subgroup (TC3 or IC3, TC3 or IC2/3, TC2/3 or IC2/3).

End point type	Secondary

End point timeframe:

Screening, Every 6 weeks (± 3 days) for 12 months following Cycle 1, Day 1 and every 9 weeks (± 1 week) thereafter until disease progression, intolerable toxicity or death until data cut-off on 28 May 2015 (Up to 16 months)

End point values	Cohort 1: First Line Atezolizumab Primary Analysis	Cohort 2: Second Line Atezolizumab Primary Analysis	Cohort 3: Third Line and Beyond Atezolizumab Primary Analysis	Cohorts 2 + 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	139	267	253	520
Units: percentage of participants				
number (confidence interval 95%)				
TC3 or IC3 Responders (n= 65, 122, 115, 237)	30.8 (19.9 to 43.5)	24.6 (17.3 to 33.2)	28.7 (20.7 to 37.9)	26.6 (21.1 to 32.7)
TC3 or IC2/3 Responders (n= 123, 247, 236, 483)	24.4 (17.1 to 33.0)	19.4 (14.7 to 24.9)	19.1 (14.3 to 24.7)	19.3 (15.8 to 23.1)
TC2/3 or IC2/3 Responders (n= 139, 267, 253, 520)	22.3 (15.7 to 30.1)	18.7 (14.2 to 23.9)	18.2 (13.6 to 23.5)	18.5 (15.2 to 22.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Objective Response Per Modified RECIST as Assessed by the INV

End point title	Percentage of Participants Achieving Objective Response Per Modified RECIST as Assessed by the INV

End point description:

ORR was the percentage of participants whose confirmed best overall response was either a PR or a CR based upon the Investigator assessment per modified RECIST. CR: disappearance of all target lesions. Any pathological lymph nodes (target or non-target) must have reduction in short axis to <10mm; PR: At least a 30% decrease in the sum of the diameters of all target and all new measurable lesions, taking as reference the baseline sum of diameters, in the absence of CR. Results were reported by line of therapy (reporting arms) and PD-L1 Expression Subgroup (TC3 or IC3, TC3 or IC2/3, TC2/3 or IC2/3).

End point type	Secondary

End point timeframe:

Screening, Every 6 weeks (± 3 days) for 12 months following Cycle 1, Day 1 and every 9 weeks (± 1 week) thereafter until disease progression, intolerable toxicity or death until data cut-off on 28 May 2015 (Up to 16 months)

End point values	Cohort 1: First Line Atezolizumab Primary Analysis	Cohort 2: Second Line Atezolizumab Primary Analysis	Cohort 3: Third Line and Beyond Atezolizumab Primary Analysis	Cohorts 2 + 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	139	267	253	520
Units: percentage of participants				
number (confidence interval 95%)				
TC3 or IC3 Responders (n= 65, 122, 115, 237)	20.0 (11.1 to 31.8)	27.0 (19.4 to 35.8)	30.4 (22.2 to 39.7)	28.7 (23.0 to 34.9)
TC3 or IC2/3 Responders (n= 123, 247, 236, 483)	16.3 (10.2 to 24.0)	21.9 (16.9 to 27.5)	20.8 (15.8 to 26.5)	21.3 (17.8 to 25.3)
TC2/3 or IC2/3 Responders (n= 139, 267, 253, 520)	15.8 (10.2 to 23.0)	21.0 (16.3 to 26.4)	19.8 (15.0 to 25.2)	20.4 (17.0 to 24.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DOR) Assessed by IRF Per RECIST v1.1

End point title	Duration of response (DOR) Assessed by IRF Per RECIST v1.1

End point description:

DOR is interval between date of first occurrence of a CR or PR that is subsequently confirmed (whichever status is recorded first) and the first date that PD or death is documented, whichever occurs first as measured by RECIST v1.1. CR: disappearance of all target and non-target lesions. Any pathological lymph nodes (target or non-target) must have reduction in short axis to <10mm; PR: > or = 30 % decrease from baseline in sum of diameters of target lesions, non-PD non-target lesions and no new lesions; PD: one or more of the following: at least 20% increase from nadir in sum of diameters of target lesions (with an absolute increase of at least 5mm), appearance of new lesions, and/or unequivocal progression of non-target lesions. DOR was assessed by Kaplan-Meier estimates. Results were reported by line of therapy (reporting arms) and PD-L1 Expression Subgroup (TC3 or IC3, TC3 or IC2/3, TC2/3 or IC2/3).

9999=N/A

End point type	Secondary

End point timeframe:

Screening, Every 6 weeks (± 3 days) for 12 months following Cycle 1, Day 1 and every 9 weeks (± 1 week) thereafter until disease progression, intolerable toxicity or death until data cut-off on 28 May 2015 (Up to 16 months)

End point values	Cohort 1: First Line Atezolizumab Primary Analysis	Cohort 2: Second Line Atezolizumab Primary Analysis	Cohort 3: Third Line and Beyond Atezolizumab Primary Analysis	Cohorts 2 + 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	139	267	253	520
Units: months				
median (confidence interval 95%)				
TC3 or IC3 DOR (n= 17, 29, 31, 60)	9999 (5.8 to 9999)	9999 (4.9 to 9999)	7.2 (5.6 to 9999)	7.2 (5.7 to 9999)
TC3 or IC2/3 DOR (n = 26, 43, 43, 86)	8.5 (5.6 to 9999)	8.4 (6.9 to 9999)	8.4 (5.7 to 9999)	8.4 (6.9 to 9999)
TC2/3 or IC2/3 DOR (n= 27, 46, 44, 90)	8.5 (5.6 to 9999)	8.4 (6.9 to 9999)	8.4 (5.7 to 9999)	8.4 (6.9 to 9999)

Statistical analyses

No statistical analyses for this end point

Secondary: DOR as Assessed by INV Per RECIST v1.1

End point title	DOR as Assessed by INV Per RECIST v1.1

End point description:

DOR is interval between date of the first occurrence of a CR or PR that is subsequently confirmed (whichever status is recorded first) and first date that PD or death is documented, whichever occurs first as measured by RECIST v1.1. CR: disappearance of all target and non-target lesions. Any pathological lymph nodes (target or non-target) must have reduction in short axis to <10mm; PR: > or = 30 % decrease from baseline in sum of diameters of target lesions, non-PD non-target lesions and no new lesions; PD: one or more of the following: at least 20% increase from nadir in sum of diameters of target lesions (with an absolute increase of at least 5mm), appearance of new lesions, and/or unequivocal progression of non-target lesions. DOR was assessed by Kaplan-Meier estimates. Results were reported by line of therapy (reporting arms) and PD-L1 Expression Subgroup (TC3 or IC3, TC3 or IC2/3, TC2/3 or IC2/3).

0000=N/A
9999=N/A

End point type	Secondary

End point timeframe:

Screening, Every 6 weeks (± 3 days) for 12 months following Cycle 1, Day 1 and every 9 weeks (± 1 week) thereafter until disease progression, intolerable toxicity or death until data cut-off on 28 May 2015 (Up to 16 months)

End point values	Cohort 1: First Line Atezolizumab Primary Analysis	Cohort 2: Second Line Atezolizumab Primary Analysis	Cohort 3: Third Line and Beyond Atezolizumab Primary Analysis	Cohorts 2 + 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	139	267	253	520
Units: months				
median (confidence interval 95%)				

TC3 or IC3 DOR (n= 20, 30, 33, 63)	8.5 (5.6 to 8.5)	9999 (8.1 to 9999)	8.4 (6.4 to 9999)	9999 (7.4 to 9999)
TC3 or IC2/3 DOR (n = 30, 48, 45, 93)	8.5 (8.5 to 9999)	9999 (0000 to 9999)	8.3 (7.0 to 9999)	9999 (8.3 to 9999)
TC2/3 or IC2/3 DOR (n= 31, 50, 46, 96)	9999 (8.5 to 9999)	9999 (0000 to 9999)	8.3 (7.0 to 9999)	9999 (8.3 to 9999)

Statistical analyses

No statistical analyses for this end point

Secondary: DOR as Assessed by INV Per Modified RECIST

End point title	DOR as Assessed by INV Per Modified RECIST

End point description:

DOR is the interval between the date of the first occurrence of a CR or PR that is subsequently confirmed (whichever status is recorded first) and the first date that PD or death is documented, whichever occurs first as measured by modified RECIST. CR: disappearance of all target lesions. Any pathological lymph nodes (target or non-target) must have reduction in short axis to <10mm; PR: at least a 30% decrease in the sum of the diameters of all target and all new measurable lesions, taking as reference the baseline sum of diameters, in the absence of CR; PD: one or more of the following: at least 20% increase from nadir in the sum of diameters of existing and/or new target lesions (with an absolute increase of at least 5mm). DOR was assessed by Kaplan-Meier estimates. Results were reported by line of therapy (reporting arms) and PD-L1 Expression Subgroup (TC3 or IC3, TC3 or IC2/3, TC2/3 or IC2/3).

0000=N/A
9999=N/A

End point type	Secondary

End point timeframe:

Screening, Every 6 weeks (± 3 days) for 12 months following Cycle 1, Day 1 and every 9 weeks (± 1 week) thereafter until disease progression, intolerable toxicity or death until data cut-off on 28 May 2015 (Up to 16 months)

End point values	Cohort 1: First Line Atezolizumab Primary Analysis	Cohort 2: Second Line Atezolizumab Primary Analysis	Cohort 3: Third Line and Beyond Atezolizumab Primary Analysis	Cohorts 2 + 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	139	267	253	520
Units: months				
median (confidence interval 95%)				
TC3 or IC3 DOR (n= 13, 33, 35, 68)	9999 (4.4 to 9999)	9999 (8.1 to 9999)	9999 (7.4 to 9999)	0000 (0000 to 8.1)
TC3 or IC2/3 DOR (n= 20, 54, 49, 103)	9999 (0000 to 9999)	9999 (0000 to 9999)	9999 (7.4 to 9999)	9999 (9999 to 9999)
TC2/3 or IC2/3 DOR (n = 22, 56, 50, 106)	9999 (4.5 to 9999)	9999 (0000 to 9999)	9999 (7.4 to 9999)	9999 (9999 to 9999)

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) as Assessed by IRF Per RECIST v1.1

End point title	Progression Free Survival (PFS) as Assessed by IRF Per RECIST v1.1

End point description:

PFS is the interval between the first dose of atezolizumab and date of disease progression or death due to any cause, whichever occurred first as measured by RECIST v1.1. PD is defined as one or more of the following: at least 20% increase from nadir in the sum of diameters of target lesions (with an absolute increase of at least 5mm), appearance of new lesions, and/or unequivocal progression of non-target lesions. PFS was assessed by Kaplan-Meier estimates.

End point type	Secondary

End point timeframe:

Screening, Every 6 weeks (± 3 days) for 12 months following Cycle 1, Day 1 and every 9 weeks (± 1 week) thereafter until disease progression, intolerable toxicity or death until data cut-off on 28 May 2015 (Up to 16 months)

End point values	Cohort 1: First Line Atezolizumab Primary Analysis	Cohort 2: Second Line Atezolizumab Primary Analysis	Cohort 3: Third Line and Beyond Atezolizumab Primary Analysis	Cohorts 2 + 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	139	267	253	520
Units: months				
median (confidence interval 95%)				
TC3 or IC3 PFS (n = 65, 122, 115, 237)	5.5 (2.7 to 8.3)	4.1 (1.8 to 5.5)	4.2 (2.8 to 5.6)	4.1 (2.8 to 5.4)
TC3 or IC2/3 PFS (n = 123, 247, 236, 483)	5.6 (3.3 to 8.3)	2.8 (1.5 to 4.0)	2.8 (2.7 to 4.0)	2.8 (2.7 to 3.0)
TC2/3 or IC2/3 PFS (n= 139, 267, 253, 520)	5.5 (3.0 to 6.9)	2.8 (1.5 to 3.5)	2.8 (2.7 to 3.7)	2.8 (2.7 to 2.9)

Statistical analyses

No statistical analyses for this end point

Secondary: PFS as Assessed by INV Per RECIST v1.1

End point title	PFS as Assessed by INV Per RECIST v1.1

End point description:

PFS is the interval between the first dose of atezolizumab and date of disease progression or death due to any cause, whichever occurred first as measured by RECIST v1.1. PD: one or more of the following: at least 20% increase from nadir in the sum of diameters of target lesions (with an absolute increase of at least 5mm), appearance of new lesions, and/or unequivocal progression of non-target lesions. PFS was assessed by Kaplan-Meier estimates.

9999=N/A

End point type	Secondary

End point timeframe:

Screening, Every 6 weeks (± 3 days) for 12 months following Cycle 1, Day 1 and every 9 weeks (± 1

week) thereafter until disease progression, intolerable toxicity or death until data cut-off on 28 May 2015 (Up to 16 months)

End point values	Cohort 1: First Line Atezolizumab Primary Analysis	Cohort 2: Second Line Atezolizumab Primary Analysis	Cohort 3: Third Line and Beyond Atezolizumab Primary Analysis	Cohorts 2 + 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	139	267	253	520
Units: months				
median (confidence interval 95%)				
TC3 or IC3 PFS (n= 65, 122, 115, 237)	7.1 (4.9 to 9999)	4.1 (2.7 to 6.5)	4.2 (3.0 to 6.2)	4.2 (2.9 to 5.6)
TC3 or IC2/3 PFS (n= 123, 247, 236, 483)	7.6 (5.9 to 9.9)	3.0 (2.7 to 4.2)	3.5 (2.8 to 4.2)	3.2 (2.8 to 4.1)
TC2/3 or IC2/3 PFS (n= 139, 267, 253, 520)	7.1 (5.6 to 8.4)	2.8 (2.6 to 4.1)	3.0 (2.8 to 4.1)	3.0 (2.8 to 4.1)

Statistical analyses

No statistical analyses for this end point

Secondary: PFS as Assessed by INV Per Modified RECIST

End point title	PFS as Assessed by INV Per Modified RECIST

End point description:

PFS is the interval between the first dose of atezolizumab and date of disease progression or death due to any cause, whichever occurred first as measured by modified RECIST. PD: at least 20% increase from nadir in the sum of diameters of new and/or existing target lesions (with an absolute increase of at least 5mm). PFS was assessed by Kaplan-Meier estimates.

9999=N/A

End point type	Secondary

End point timeframe:

Screening, Every 6 weeks (± 3 days) for 12 months following Cycle 1, Day 1 and every 9 weeks (± 1 week) thereafter until disease progression, intolerable toxicity or death until data cut-off on 28 May 2015 (Up to 16 months)

End point values	Cohort 1: First Line Atezolizumab Primary Analysis	Cohort 2: Second Line Atezolizumab Primary Analysis	Cohort 3: Third Line and Beyond Atezolizumab Primary Analysis	Cohorts 2 + 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	139	267	253	520
Units: months				
median (confidence interval 95%)				

TC3 or IC3 PFS (n= 65, 122, 115, 237)	7.1 (4.7 to 9999)	5.7 (4.1 to 8.4)	6.3 (4.1 to 8.1)	5.8 (4.3 to 7.1)
TC3 or IC2/3 PFS (n= 123, 247, 236, 483)	7.9 (5.7 to 10.0)	4.5 (4.0 to 6.0)	4.9 (4.1 to 6.8)	4.6 (4.1 to 5.7)
TC2/3 or IC2/3 PFS (n= 139, 267, 253, 520)	7.6 (5.6 to 9.9)	4.2 (3.9 to 5.7)	4.6 (4.1 to 6.3)	4.4 (4.1 to 5.5)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival : Percentage of Participants Without Event (Death)

End point title	Overall Survival : Percentage of Participants Without Event (Death)

End point description:

End point type	Secondary

End point timeframe:

Screening, Every 6 weeks (± 3 days) for 12 months following Cycle 1, Day 1 and every 9 weeks (± 1 week) thereafter until disease progression, intolerable toxicity or death until data cut-off on 28 May 2015 (Up to 16 months)

End point values	Cohort 1: First Line Atezolizumab Primary Analysis	Cohort 2: Second Line Atezolizumab Primary Analysis	Cohort 3: Third Line and Beyond Atezolizumab Primary Analysis	Cohorts 2 + 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	139	267	253	520
Units: percentage of participants				
number (not applicable)				
TC3 or IC3 (n=65, 122, 115, 237)	70.8	70.5	67.0	68.8
TC3 or IC2/3 (n= 123, 247, 236, 483)	75.6	69.2	60.6	65.0
TC2/3 or IC2/3 (n= 139, 267, 253, 520)	74.1	67.4	60.5	64.0

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival : Median Time to Event (Death)

End point title	Overall Survival : Median Time to Event (Death)

End point description:

Overall survival is measured as interval between the first dose of atezolizumab and date of death from any cause.

9999=N/A

End point type	Secondary

End point timeframe:

Screening, Every 6 weeks (± 3 days) for 12 months following Cycle 1, Day 1 and every 9 weeks (± 1 week) thereafter until disease progression, intolerable toxicity or death until data cut-off on 28 May 2015 (Up to 16 months)

End point values	Cohort 1: First Line Atezolizumab Primary Analysis	Cohort 2: Second Line Atezolizumab Primary Analysis	Cohort 3: Third Line and Beyond Atezolizumab Primary Analysis	Cohorts 2 + 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	139	267	253	520
Units: months				
median (confidence interval 95%)				
TC3 or IC3 (n= 65, 122, 115, 237)	9999 (10.4 to 9999)	9999 (10.6 to 9999)	9999 (0000 to 9999)	9999 (12.1 to 9999)
TC3 or IC2/3 (n= 123, 247, 236, 483)	14.0 (14.0 to 9999)	9999 (12.1 to 9999)	9999 (8.4 to 9999)	9999 (12.1 to 9999)
TC2/3 or IC2/3 (n= 139, 267, 253, 520)	14.0 (14.0 to 9999)	9999 (11.2 to 9999)	9999 (8.4 to 9999)	9999 (12.1 to 9999)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Without an Event (Death) at 6 Months

End point title	Percentage of Participants Without an Event (Death) at 6 Months

End point description:

End point type	Secondary

End point timeframe:

Month 6

End point values	Cohort 1: First Line Atezolizumab Primary Analysis	Cohort 2: Second Line Atezolizumab Primary Analysis	Cohort 3: Third Line and Beyond Atezolizumab Primary Analysis	Cohorts 2 + 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	139	267	253	520
Units: percentage of participants				
number (confidence interval 95%)				
TC3 or IC3 (n= 65, 122, 115, 237)	79.2 (69.1 to 89.3)	79.7 (72.5 to 87.0)	75.1 (67.1 to 83.1)	77.4 (72.0 to 82.8)
TC3 or IC2/3 (n= 123, 247, 236, 483)	83.9 (77.2 to 90.5)	78.1 (72.8 to 83.4)	71.0 (65.2 to 76.9)	74.6 (70.6 to 78.5)

TC2/3 or IC2/3 (n= 139, 267, 253, 520)	81.7 (75.1 to 88.4)	76.2 (71.0 to 81.5)	70.5 (64.9 to 76.2)	73.4 (69.5 to 77.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Without an Event (Death) at 12 Months

End point title	Percentage of Participants Without an Event (Death) at 12 Months

End point description:

End point type	Secondary

End point timeframe:

Month 12

End point values	Cohort 1: First Line Atezolizumab Primary Analysis	Cohort 2: Second Line Atezolizumab Primary Analysis	Cohort 3: Third Line and Beyond Atezolizumab Primary Analysis	Cohorts 2 + 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	139	267	253	520
Units: percentage of participants				
number (confidence interval 95%)				
TC3 or IC3 (n= 65, 122, 115, 237)	58.6 (40.7 to 76.5)	61.5 (49.0 to 74.0)	62.6 (52.8 to 72.5)	61.3 (52.7 to 69.8)
TC3 or IC2/3 (n= 123, 247, 236, 483)	67.1 (55.7 to 78.4)	59.3 (50.5 to 68.1)	54.9 (47.7 to 62.2)	56.3 (50.6 to 62.5)
TC2/3 or IC2/3 (n=139, 267, 253, 520)	65.0 (54.0 to 76.1)	57.2 (48.6 to 65.7)	54.4 (47.3 to 61.5)	55.3 (49.5 to 61.1)

Statistical analyses

No statistical analyses for this end point

Secondary: PFS: Percentage of Participants Alive and Progression Free at 6 Months

End point title	PFS: Percentage of Participants Alive and Progression Free at 6 Months

End point description:

PD is defined as one or more of the following: at least 20% increase from nadir in the sum of diameters of target lesions (with an absolute increase of at least 5mm), appearance of new lesions, and/or unequivocal progression of non-target lesions.

End point type	Secondary

End point timeframe:

Month 6

End point values	Cohort 1: First Line Atezolizumab Primary Analysis	Cohort 2: Second Line Atezolizumab Primary Analysis	Cohort 3: Third Line and Beyond Atezolizumab Primary Analysis	Cohorts 2 + 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	139	267	253	520
Units: percentage of participants				
number (confidence interval 95%)				
TC3 or IC3 (n= 65, 122, 115, 237)	57.4 (44.7 to 70.1)	41.3 (32.3 to 50.4)	42.1 (33.1 to 51.2)	41.8 (35.4 to 48.2)
TC3 or IC2/3 (n= 123, 247, 236, 483)	58.6 (49.5 to 67.8)	36.1 (29.9 to 42.2)	35.8 (29.6 to 41.9)	35.9 (31.6 to 40.3)
TC2/3 or IC2/3 (n= 139, 267, 253, 520)	56.4 (47.8 to 65.1)	34.8 (29.0 to 40.7)	34.7 (28.7 to 40.6)	34.8 (30.6 to 38.9)

Statistical analyses

No statistical analyses for this end point

Secondary: PFS: Percentage of Participants Alive and Progression Free at 12 Months

End point title	PFS: Percentage of Participants Alive and Progression Free at 12 Months

End point description:

PD is defined as one or more of the following: at least 20% increase from nadir in the sum of diameters of target lesions (with an absolute increase of at least 5mm), appearance of new lesions, and/or unequivocal progression of non-target lesions.

End point type	Secondary

End point timeframe:

Month 12

End point values	Cohort 1: First Line Atezolizumab Primary Analysis	Cohort 2: Second Line Atezolizumab Primary Analysis	Cohort 3: Third Line and Beyond Atezolizumab Primary Analysis	Cohorts 2 + 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	139	267	253	520
Units: percentage of participants				
number (confidence interval 95%)				
TC3 or IC3 (n= 65, 122, 115, 237)	33.1 (14.9 to 51.3)	27.8 (17.6 to 37.9)	16.1 (3.8 to 28.5)	23.1 (15.4 to 30.8)
TC3 or IC2/3 (n= 123, 247, 236, 483)	29.0 (13.1 to 45.0)	22.7 (16.1 to 29.3)	15.1 (8.3 to 21.8)	19.1 (14.4 to 23.8)

TC2/3 or IC2/3 (n= 139, 267, 253, 520)	26.9 (12.1 to 41.7)	21.8 (15.5 to 28.1)	14.7 (8.1 to 21.3)	18.5 (14.0 to 23.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Time in Response (TIR) as Assessed by INV Per RECIST v1.1

End point title	Time in Response (TIR) as Assessed by INV Per RECIST v1.1

End point description:

TIR is interval between date of first occurrence of a CR or PR that is subsequently confirmed (whichever status is recorded first) and first date that PD or death is documented, whichever occurs first as measured by RECIST v1.1. For responders, TIR was the same as DOR; for non-responders, TIR was considered as an event and defined as the date of first treatment plus one day. TIR was assessed by Kaplan-Meier estimates.

0000=N/A
9999=N/A

End point type	Secondary

End point timeframe:

Screening, Every 6 weeks (± 3 days) for 12 months following Cycle 1, Day 1 and every 9 weeks (± 1 week) thereafter until disease progression, intolerable toxicity or death until data cut-off on 28 May 2015 (Up to 16 months)

End point values	Cohort 1: First Line Atezolizumab Primary Analysis	Cohort 2: Second Line Atezolizumab Primary Analysis	Cohort 3: Third Line and Beyond Atezolizumab Primary Analysis	Cohorts 2 + 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	139	267	253	520
Units: months				
median (confidence interval 95%)	0.033 (0000 to 9999)	0.033 (0000 to 9999)	0.033 (0000 to 9999)	0.033 (0000 to 9999)

Statistical analyses

No statistical analyses for this end point

Secondary: TIR as Assessed by INV Per Modified RECIST

End point title	TIR as Assessed by INV Per Modified RECIST

End point description:

TIR is interval between date of first occurrence of a CR or PR that is subsequently confirmed (whichever status is recorded first) and first date that PD or death is documented, whichever occurs first as measured by modified RECIST. For responders, TIR was the same as DOR; for non-responders, TIR was considered as an event and defined as the date of first treatment plus one day. TIR was assessed by Kaplan-Meier estimates.

0000=N/A
9999=N/A

End point type	Secondary

End point timeframe:

Screening, Every 6 weeks (± 3 days) for 12 months following Cycle 1, Day 1 and every 9 weeks (± 1 week) thereafter until disease progression, intolerable toxicity or death until data cut-off on 28 May 2015 (Up to 16 months)

End point values	Cohort 1: First Line Atezolizumab Primary Analysis	Cohort 2: Second Line Atezolizumab Primary Analysis	Cohort 3: Third Line and Beyond Atezolizumab Primary Analysis	Cohorts 2 + 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	139	267	253	520
Units: months				
median (confidence interval 95%)	0.033 (0000 to 9999)	0.033 (0000 to 9999)	0.033 (0000 to 9999)	0.033 (0000 to 9999)

Statistical analyses

No statistical analyses for this end point

Secondary: TIR as Assessed by IRF Per RECIST v1.1

End point title	TIR as Assessed by IRF Per RECIST v1.1

End point description:

TIR is interval between date of first occurrence of a CR or PR that is subsequently confirmed (whichever status is recorded first) and first date that PD or death is documented, whichever occurs first as measured by RECIST v1.1. For responders, TIR was the same as DOR; for non-responders, TIR was considered as an event and defined as the date of first treatment plus one day. TIR was assessed by Kaplan-Meier estimates.

0000=N/A
9999=N/A

End point type	Secondary

End point timeframe:

Screening, Every 6 weeks (± 3 days) for 12 months following Cycle 1, Day 1 and every 9 weeks (± 1 week) thereafter until disease progression, intolerable toxicity or death until data cut-off on 28 May 2015 (Up to 16 months)

End point values	Cohort 1: First Line Atezolizumab Primary Analysis	Cohort 2: Second Line Atezolizumab Primary Analysis	Cohort 3: Third Line and Beyond Atezolizumab Primary Analysis	Cohorts 2 + 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	139	267	253	520

Units: months				
median (confidence interval 95%)	0.033 (0000 to 9999)	0.033 (0000 to 9999)	0.033 (0000 to 9999)	0.033 (0000 to 9999)

Statistical analyses

No statistical analyses for this end point

Secondary: Atezolizumab Serum Concentrations

End point title	Atezolizumab Serum Concentrations

End point description:

Serum concentrations were determined for all participants after administration of atezolizumab up to Cycle 8. Time (T) = time from first dose in days.

End point type	Secondary

End point timeframe:

Pre-dose (hour 0) and 0.5 hours post dose on Cycle 1 Day 1 (Cycle length = 21days), Cycle 1 Days 2, 4, 8, 15, and 21, Cycle 2 Day 21, Cycle 3 Day 21, Cycle 7 Day 21

End point values	Pharmacokinetic Evaluable Population			
Subject group type	Subject analysis set			
Number of subjects analysed	646			
Units: micrograms per milliliter (µg/mL)				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 T=0 (n=646)	0.285 (± 4.35)			
Cycle 1 Day 1 T=0.021 (n=624)	429.0 (± 218)			
Cycle 1 Day 2 T=1 (n=47)	299.0 (± 65.3)			
Cycle 1 Day 4 T=3 (n=44)	220.0 (± 48.4)			
Cycle 1 Day 8 T=7 (n=38)	155.0 (± 35.4)			
Cycle 1 Day 15 T=14 (n=36)	106.0 (± 32.1)			
Cycle 1 Day 21 T=21 (n=596)	87.8 (± 41.7)			
Cycle 2 Day 21 T=42 (n=518)	134.0 (± 57.2)			
Cycle 3 Day 21 T=63 (n=467)	163.0 (± 70.7)			
Cycle 7 Day 21 T=147 (n=275)	212.0 (± 88.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Positive Anti-Therapeutic Antibody (Anti-Atezolizumab Antibody) Status

End point title	Percentage of Participants with Positive Anti-Therapeutic Antibody (Anti-Atezolizumab Antibody) Status

End point description:

Anti-therapeutic antibodies is a measurement to explore the potential relationship of immunogenicity response with pharmacokinetics, safety and efficacy.

End point type	Secondary

End point timeframe:

Baseline, post-baseline (up to 16 months)

End point values	Cohort 1: First Line Atezolizumab Primary Analysis	Cohort 2: Second Line Atezolizumab Primary Analysis	Cohort 3: Third Line and Beyond Atezolizumab Primary Analysis	Cohorts 2 + 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	139	267	253	520
Units: percentage of participants				
number (not applicable)				
Baseline (n=135,257,247,504)	7.4	3.5	6.1	4.8
Post-Baseline (n=133,253,238,491)	45.1	36.0	37.4	36.7

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Event (Disease Progression or Death) as Assessed by IRF Per RECIST v1.1

End point title	Percentage of Participants with Event (Disease Progression or Death) as Assessed by IRF Per RECIST v1.1

End point description:

PD was defined as one or more of the following: at least 20% increase from nadir in the sum of diameters of target lesions (with an absolute increase of at least 5 mm), appearance of new lesions, and/or unequivocal progression of non-target lesions.

End point type	Secondary

End point timeframe:

Screening, Every 6 weeks (± 3 days) for 12 months following Cycle 1, Day 1 and every 9 weeks (± 1 week) thereafter until disease progression, intolerable toxicity or death until data cut-off on 28 May 2015 (Up to 16 months)

End point values	Cohort 1: First Line Atezolizumab Primary Analysis	Cohort 2: Second Line Atezolizumab Primary Analysis	Cohort 3: Third Line and Beyond Atezolizumab Primary Analysis	Cohorts 2 + 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	139	267	253	520
Units: percentage of participants				
number (not applicable)				

TC3 or IC3 (n= 65, 122, 115, 237)	58.5	68.0	73.0	70.5
TC3 or IC2/3 (n= 123, 247, 236, 483)	61.8	73.7	79.2	76.4
TC2/3 or IC2/3 (n= 139, 27, 253, 520)	63.3	75.3	79.1	77.1

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Event (Disease Progression or Death) as Assessed by INV Per RECIST v1.1

End point title	Percentage of Participants with Event (Disease Progression or Death) as Assessed by INV Per RECIST v1.1

End point description:

PD was defined as one or more of the following: at least 20% increase from nadir in the sum of diameters of target lesions (with an absolute increase of at least 5 mm), appearance of new lesions, and/or unequivocal progression of non-target lesions.

End point type	Secondary

End point timeframe:

Screening, Every 6 weeks (± 3 days) for 12 months following Cycle 1, Day 1 and every 9 weeks (± 1 week) thereafter until disease progression, intolerable toxicity or death until data cut-off on 28 May 2015 (Up to 16 months)

End point values	Cohort 1: First Line Atezolizumab Primary Analysis	Cohort 2: Second Line Atezolizumab Primary Analysis	Cohort 3: Third Line and Beyond Atezolizumab Primary Analysis	Cohorts 2 + 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	139	267	253	520
Units: percentage of participants				
number (not applicable)				
TC3 or IC3 (n= 65, 122, 115, 237)	50.8	63.1	68.7	65.8
TC3 or IC2/3 (n= 123, 247, 236, 483)	50.4	68.8	74.6	71.6
TC2/3 or IC2/3 (n= 139, 267, 253, 520)	52.5	70.0	74.7	72.3

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Event (Disease Progression or Death) as Assessed by INV Per Modified RECIST v1.1

End point title	Percentage of Participants with Event (Disease Progression or Death) as Assessed by INV Per Modified RECIST v1.1

End point description:

PD was defined as at least 20% increase from nadir in the sum of diameters of new and/or existing target lesions (with an absolute increase of at least 5 mm).

End point type	Secondary

End point timeframe:

Screening, Every 6 weeks (± 3 days) for 12 months following Cycle 1, Day 1 and every 9 weeks (± 1 week) thereafter until disease progression, intolerable toxicity or death until data cut-off on 28 May 2015 (Up to 16 months)

End point values	Cohort 1: First Line Atezolizumab Primary Analysis	Cohort 2: Second Line Atezolizumab Primary Analysis	Cohort 3: Third Line and Beyond Atezolizumab Primary Analysis	Cohorts 2 + 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	139	267	253	520
Units: percentage of participants				
number (not applicable)				
TC3 or IC3 (n= 65, 122, 115, 237)	36.9	56.6	60.0	58.2
TC3 or IC2/3 (n= 123, 247, 236, 483)	38.2	61.5	66.1	63.8
TC2/3 or IC2/3 (n= 139, 267, 253, 520)	39.6	62.9	66.4	64.6

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded from the date of Screening until 30 days after the final follow-up visit until data cut-off on 11 January 2019 (up to 60 months)

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Cohort 1: First Line Atezolizumab

Reporting group description:

Participants received 1200 milligrams (mg) atezolizumab every 3 weeks (Day 1 of 21 day cycle) administered by intravenous (IV) infusion until intolerable toxicity, disease progression or death. Participants in this cohort received no prior chemotherapy in locally advanced or metastatic setting.

Reporting group title	Cohort 2: Second Line Atezolizumab

Reporting group description:

Participants received 1200 mg atezolizumab every 3 weeks (Day 1 of 21-day cycle) administered by IV infusion until intolerable toxicity, disease progression or death. Participants were permitted to continue treatment after progressive disease, if the following criteria were met: evidence of clinical benefit as assessed by the investigator; absence of symptoms and signs indicating unequivocal progression of disease; no decline in Eastern Cooperative Oncology Group (ECOG) performance status; absence of tumor growth at critical anatomical sites that cannot be managed by protocol-allowed medical interventions; evidence of clinical benefit as assessed by the investigator. Participants in this cohort progressed during or after prior platinum-based chemotherapy in locally advanced or metastatic setting.

Reporting group title	Cohort 3: Third Line and Beyond Atezolizumab

Reporting group description:

Participants received 1200 mg atezolizumab every 3 weeks (Day 1 of 21-day cycle) administered by IV infusion until intolerable toxicity, disease progression or death. Participants were permitted to continue treatment after progressive disease, if the following criteria were met: absence of symptoms and signs indicating unequivocal progression of disease; no decline in ECOG performance status; absence of tumor growth at critical anatomical sites that cannot be managed by protocol-allowed medical interventions; evidence of clinical benefit as assessed by the investigator. Participants in this cohort progressed during or after prior platinum-based chemotherapy and at least one additional therapy in locally advanced or metastatic setting.

Serious adverse events	Cohort 1: First Line Atezolizumab	Cohort 2: Second Line Atezolizumab	Cohort 3: Third Line and Beyond Atezolizumab
Total subjects affected by serious adverse events			
subjects affected / exposed	47 / 138 (34.06%)	117 / 269 (43.49%)	113 / 252 (44.84%)
number of deaths (all causes)	89	193	198
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ACUTE MYELOID LEUKAEMIA			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

ADENOCARCINOMA OF COLON			
subjects affected / exposed	1 / 138 (0.72%)	0 / 269 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BLADDER CANCER			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COLON CANCER			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GLIOBLASTOMA MULTIFORME			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
INVASIVE DUCTAL BREAST CARCINOMA			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LYMPHANGIOSIS CARCINOMATOSA			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MALIGNANT PLEURAL EFFUSION			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
METASTASES TO CENTRAL NERVOUS SYSTEM			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERICARDIAL EFFUSION MALIGNANT			

subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PLEURAL MESOTHELIOMA MALIGNANT			
subjects affected / exposed	1 / 138 (0.72%)	0 / 269 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RECTAL ADENOCARCINOMA			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL CANCER			
subjects affected / exposed	1 / 138 (0.72%)	0 / 269 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL CELL CARCINOMA			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SMALL CELL LUNG CANCER			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
TRANSITIONAL CELL CARCINOMA			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TUMOUR PAIN			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
DEEP VEIN THROMBOSIS			

subjects affected / exposed	1 / 138 (0.72%)	2 / 269 (0.74%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EMBOLISM			
subjects affected / exposed	1 / 138 (0.72%)	0 / 269 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMATOMA			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERTENSION			
subjects affected / exposed	0 / 138 (0.00%)	2 / 269 (0.74%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOTENSION			
subjects affected / exposed	1 / 138 (0.72%)	0 / 269 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTERNAL HAEMORRHAGE			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
JUGULAR VEIN THROMBOSIS			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ORTHOSTATIC HYPOTENSION			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERIPHERAL ARTERY OCCLUSION			

subjects affected / exposed	1 / 138 (0.72%)	0 / 269 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PHLEBITIS			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
SUPERIOR VENA CAVA SYNDROME			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
ALCOHOL DETOXIFICATION			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DRUG DETOXIFICATION			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	1 / 138 (0.72%)	1 / 269 (0.37%)	3 / 252 (1.19%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHEST PAIN			
subjects affected / exposed	0 / 138 (0.00%)	2 / 269 (0.74%)	2 / 252 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHILLS			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

DEATH			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
FATIGUE			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERTHERMIA			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MALAISE			
subjects affected / exposed	0 / 138 (0.00%)	2 / 269 (0.74%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PAIN			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYREXIA			

subjects affected / exposed	1 / 138 (0.72%)	9 / 269 (3.35%)	8 / 252 (3.17%)
occurrences causally related to treatment / all	1 / 1	2 / 9	3 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUDDEN DEATH			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Reproductive system and breast disorders			
PELVIC PAIN			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SCROTAL PAIN			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
ACQUIRED TRACHEO-OESOPHAGEAL FISTULA			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ACUTE RESPIRATORY FAILURE			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ASPIRATION			
subjects affected / exposed	1 / 138 (0.72%)	0 / 269 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRONCHIAL HAEMORRHAGE			

subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRONCHIAL OBSTRUCTION			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHRONIC OBSTRUCTIVE PULMONARY DISEASE			
subjects affected / exposed	1 / 138 (0.72%)	2 / 269 (0.74%)	4 / 252 (1.59%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COUGH			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	2 / 252 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSPNOEA			
subjects affected / exposed	3 / 138 (2.17%)	5 / 269 (1.86%)	11 / 252 (4.37%)
occurrences causally related to treatment / all	0 / 3	2 / 6	0 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMOPTYSIS			
subjects affected / exposed	2 / 138 (1.45%)	2 / 269 (0.74%)	4 / 252 (1.59%)
occurrences causally related to treatment / all	1 / 2	0 / 6	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOXIA			
subjects affected / exposed	1 / 138 (0.72%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTERSTITIAL LUNG DISEASE			
subjects affected / exposed	1 / 138 (0.72%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LARYNGEAL HAEMORRHAGE			

subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PLEURAL EFFUSION			
subjects affected / exposed	1 / 138 (0.72%)	1 / 269 (0.37%)	3 / 252 (1.19%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
PNEUMONIA ASPIRATION			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	2 / 252 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
PNEUMONITIS			
subjects affected / exposed	2 / 138 (1.45%)	6 / 269 (2.23%)	6 / 252 (2.38%)
occurrences causally related to treatment / all	2 / 2	5 / 6	4 / 7
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
PNEUMOTHORAX			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY EMBOLISM			
subjects affected / exposed	2 / 138 (1.45%)	2 / 269 (0.74%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	1 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY HAEMORRHAGE			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY OEDEMA			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RESPIRATORY DISTRESS			

subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	3 / 252 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
RESPIRATORY FAILURE			
subjects affected / exposed	1 / 138 (0.72%)	1 / 269 (0.37%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
TRACHEAL STENOSIS			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
CONFUSIONAL STATE			
subjects affected / exposed	1 / 138 (0.72%)	2 / 269 (0.74%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DISORIENTATION			
subjects affected / exposed	0 / 138 (0.00%)	2 / 269 (0.74%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MENTAL STATUS CHANGES			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BLOOD LACTATE DEHYDROGENASE INCREASED			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

GAMMA-GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEPATIC ENZYME INCREASED			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
ALLERGIC TRANSFUSION REACTION			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FALL			
subjects affected / exposed	1 / 138 (0.72%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEMUR FRACTURE			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	2 / 252 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INCISIONAL HERNIA			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFUSION RELATED REACTION			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LOWER LIMB FRACTURE			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

THORACIC VERTEBRAL FRACTURE			
subjects affected / exposed	1 / 138 (0.72%)	0 / 269 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TRAUMATIC HAEMOTHORAX			
subjects affected / exposed	1 / 138 (0.72%)	0 / 269 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
ACUTE CORONARY SYNDROME			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	1 / 138 (0.72%)	0 / 269 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANGINA PECTORIS			
subjects affected / exposed	1 / 138 (0.72%)	0 / 269 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATRIAL FIBRILLATION			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	2 / 252 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATRIAL FLUTTER			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATRIOVENTRICULAR BLOCK COMPLETE			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

ATRIOVENTRICULAR BLOCK SECOND DEGREE			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIAC ARREST			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
CARDIAC FAILURE			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	2 / 252 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
CARDIAC TAMPONADE			
subjects affected / exposed	1 / 138 (0.72%)	2 / 269 (0.74%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 1	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MYOCARDIAL INFARCTION			
subjects affected / exposed	1 / 138 (0.72%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERICARDIAL EFFUSION			
subjects affected / exposed	1 / 138 (0.72%)	0 / 269 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TACHYCARDIA			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VENTRICULAR FIBRILLATION			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

APRAXIA			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CEREBRAL INFARCTION			
subjects affected / exposed	1 / 138 (0.72%)	0 / 269 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	1 / 138 (0.72%)	2 / 269 (0.74%)	3 / 252 (1.19%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
DYSARTHRIA			
subjects affected / exposed	0 / 138 (0.00%)	2 / 269 (0.74%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
FACIAL PARALYSIS			
subjects affected / exposed	1 / 138 (0.72%)	0 / 269 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMORRHAGE INTRACRANIAL			
subjects affected / exposed	1 / 138 (0.72%)	0 / 269 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEADACHE			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ISCHAEMIC STROKE			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MIGRAINE			

subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MOTOR DYSFUNCTION			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MYELOPATHY			
subjects affected / exposed	1 / 138 (0.72%)	0 / 269 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PARAPLEGIA			
subjects affected / exposed	1 / 138 (0.72%)	0 / 269 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PRESYNCOPE			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SOMNOLENCE			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPINAL CORD COMPRESSION			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SYNCOPE			
subjects affected / exposed	0 / 138 (0.00%)	3 / 269 (1.12%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TRANSIENT ISCHAEMIC ATTACK			

subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VOCAL CORD PARALYSIS			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
LYMPHADENITIS			
subjects affected / exposed	1 / 138 (0.72%)	0 / 269 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPLENIC INFARCTION			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
THROMBOCYTOPENIA			
subjects affected / exposed	1 / 138 (0.72%)	0 / 269 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	2 / 252 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ASCITES			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COLITIS			

subjects affected / exposed	1 / 138 (0.72%)	1 / 269 (0.37%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CONSTIPATION			
subjects affected / exposed	2 / 138 (1.45%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIARRHOEA			
subjects affected / exposed	2 / 138 (1.45%)	2 / 269 (0.74%)	2 / 252 (0.79%)
occurrences causally related to treatment / all	0 / 2	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSPHAGIA			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTRIC ULCER HAEMORRHAGE			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTRITIS			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	0 / 138 (0.00%)	2 / 269 (0.74%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMATEMESIS			

subjects affected / exposed	0 / 138 (0.00%)	2 / 269 (0.74%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NAUSEA			
subjects affected / exposed	1 / 138 (0.72%)	3 / 269 (1.12%)	2 / 252 (0.79%)
occurrences causally related to treatment / all	1 / 1	3 / 5	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OESOPHAGEAL PERFORATION			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OESOPHAGEAL STENOSIS			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OESOPHAGEAL VARICES HAEMORRHAGE			
subjects affected / exposed	1 / 138 (0.72%)	0 / 269 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANCREATITIS			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANCREATITIS ACUTE			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VOMITING			

subjects affected / exposed	0 / 138 (0.00%)	4 / 269 (1.49%)	3 / 252 (1.19%)
occurrences causally related to treatment / all	0 / 0	2 / 7	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
CHOLECYSTITIS			
subjects affected / exposed	1 / 138 (0.72%)	0 / 269 (0.00%)	2 / 252 (0.79%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEPATIC FAILURE			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
HEPATIC HAEMORRHAGE			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEPATOMEGALY			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
DERMATOMYOSITIS			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DRUG ERUPTION			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	2 / 252 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

CALCULUS URINARY			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMORRHAGE URINARY TRACT			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEPHROLITHIASIS			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL INFARCT			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
ADRENAL INSUFFICIENCY			
subjects affected / exposed	1 / 138 (0.72%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOTHYROIDISM			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
BACK PAIN			
subjects affected / exposed	0 / 138 (0.00%)	2 / 269 (0.74%)	2 / 252 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BONE PAIN			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	2 / 252 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

GOUTY ARTHRITIS			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTERVERTEBRAL DISC COMPRESSION			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	2 / 252 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MUSCULAR WEAKNESS			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MYALGIA			
subjects affected / exposed	1 / 138 (0.72%)	0 / 269 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PAIN IN EXTREMITY			
subjects affected / exposed	1 / 138 (0.72%)	0 / 269 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PATHOLOGICAL FRACTURE			
subjects affected / exposed	1 / 138 (0.72%)	2 / 269 (0.74%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPINAL PAIN			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			

BACTERAEMIA			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRONCHITIS			
subjects affected / exposed	2 / 138 (1.45%)	1 / 269 (0.37%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CATHETER SITE INFECTION			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CLOSTRIDIUM DIFFICILE COLITIS			
subjects affected / exposed	1 / 138 (0.72%)	0 / 269 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIVERTICULITIS			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EMPYEMA			
subjects affected / exposed	1 / 138 (0.72%)	0 / 269 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ENCEPHALITIS			
subjects affected / exposed	1 / 138 (0.72%)	0 / 269 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ENTEROCOLITIS INFECTIOUS			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ESCHERICHIA URINARY TRACT INFECTION			

subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEBRILE INFECTION			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROINTESTINAL INFECTION			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFECTION			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	2 / 252 (0.79%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFECTIOUS PLEURAL EFFUSION			
subjects affected / exposed	1 / 138 (0.72%)	0 / 269 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFLUENZA			
subjects affected / exposed	1 / 138 (0.72%)	0 / 269 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LARGE INTESTINE INFECTION			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 138 (0.00%)	2 / 269 (0.74%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUNG ABSCESS			

subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUNG INFECTION			
subjects affected / exposed	1 / 138 (0.72%)	3 / 269 (1.12%)	2 / 252 (0.79%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
MEDIASTINITIS			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OSTEOMYELITIS			
subjects affected / exposed	1 / 138 (0.72%)	0 / 269 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERITONITIS			
subjects affected / exposed	1 / 138 (0.72%)	0 / 269 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA			
subjects affected / exposed	6 / 138 (4.35%)	15 / 269 (5.58%)	16 / 252 (6.35%)
occurrences causally related to treatment / all	0 / 6	0 / 19	1 / 18
deaths causally related to treatment / all	0 / 0	0 / 1	1 / 2
PNEUMONIA BACTERIAL			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA PNEUMOCOCCAL			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA PSEUDOMONAL			

subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYELONEPHRITIS			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEPSIS			
subjects affected / exposed	0 / 138 (0.00%)	2 / 269 (0.74%)	2 / 252 (0.79%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEPTIC SHOCK			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
SUBCUTANEOUS ABSCESS			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 138 (0.72%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 138 (0.72%)	1 / 269 (0.37%)	3 / 252 (1.19%)
occurrences causally related to treatment / all	1 / 1	0 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VESTIBULAR NEURONITIS			

subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VIRAL UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 138 (0.72%)	0 / 269 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	0 / 138 (0.00%)	0 / 269 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEHYDRATION			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FAILURE TO THRIVE			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERCALCAEMIA			
subjects affected / exposed	0 / 138 (0.00%)	6 / 269 (2.23%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	2 / 7	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPONATRAEMIA			
subjects affected / exposed	0 / 138 (0.00%)	3 / 269 (1.12%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TYPE 2 DIABETES MELLITUS			
subjects affected / exposed	0 / 138 (0.00%)	1 / 269 (0.37%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Cohort 1: First Line Atezolizumab	Cohort 2: Second Line Atezolizumab	Cohort 3: Third Line and Beyond Atezolizumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	116 / 138 (84.06%)	229 / 269 (85.13%)	229 / 252 (90.87%)
Investigations			
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	3 / 138 (2.17%)	14 / 269 (5.20%)	12 / 252 (4.76%)
occurrences (all)	3	17	17
BLOOD CREATININE INCREASED			
subjects affected / exposed	4 / 138 (2.90%)	16 / 269 (5.95%)	6 / 252 (2.38%)
occurrences (all)	4	22	7
WEIGHT DECREASED			
subjects affected / exposed	7 / 138 (5.07%)	22 / 269 (8.18%)	29 / 252 (11.51%)
occurrences (all)	7	28	35
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	7 / 138 (5.07%)	27 / 269 (10.04%)	21 / 252 (8.33%)
occurrences (all)	9	39	25
HEADACHE			
subjects affected / exposed	19 / 138 (13.77%)	22 / 269 (8.18%)	35 / 252 (13.89%)
occurrences (all)	25	33	43
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	17 / 138 (12.32%)	31 / 269 (11.52%)	22 / 252 (8.73%)
occurrences (all)	33	54	41
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	13 / 138 (9.42%)	27 / 269 (10.04%)	40 / 252 (15.87%)
occurrences (all)	19	49	87
CHEST PAIN			
subjects affected / exposed	5 / 138 (3.62%)	24 / 269 (8.92%)	26 / 252 (10.32%)
occurrences (all)	7	30	30
CHILLS			

subjects affected / exposed	5 / 138 (3.62%)	15 / 269 (5.58%)	14 / 252 (5.56%)
occurrences (all)	5	18	15
FATIGUE			
subjects affected / exposed	52 / 138 (37.68%)	85 / 269 (31.60%)	92 / 252 (36.51%)
occurrences (all)	70	145	142
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	13 / 138 (9.42%)	24 / 269 (8.92%)	13 / 252 (5.16%)
occurrences (all)	17	30	18
MALAISE			
subjects affected / exposed	9 / 138 (6.52%)	8 / 269 (2.97%)	9 / 252 (3.57%)
occurrences (all)	10	10	9
MUCOSAL INFLAMMATION			
subjects affected / exposed	7 / 138 (5.07%)	11 / 269 (4.09%)	10 / 252 (3.97%)
occurrences (all)	7	13	17
OEDEMA PERIPHERAL			
subjects affected / exposed	10 / 138 (7.25%)	22 / 269 (8.18%)	22 / 252 (8.73%)
occurrences (all)	11	32	26
PAIN			
subjects affected / exposed	11 / 138 (7.97%)	15 / 269 (5.58%)	11 / 252 (4.37%)
occurrences (all)	17	19	12
PYREXIA			
subjects affected / exposed	20 / 138 (14.49%)	47 / 269 (17.47%)	45 / 252 (17.86%)
occurrences (all)	24	63	60
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	10 / 138 (7.25%)	22 / 269 (8.18%)	18 / 252 (7.14%)
occurrences (all)	12	27	24
ABDOMINAL PAIN UPPER			
subjects affected / exposed	5 / 138 (3.62%)	6 / 269 (2.23%)	15 / 252 (5.95%)
occurrences (all)	7	7	18
CONSTIPATION			
subjects affected / exposed	19 / 138 (13.77%)	47 / 269 (17.47%)	45 / 252 (17.86%)
occurrences (all)	27	57	57
DIARRHOEA			
subjects affected / exposed	29 / 138 (21.01%)	64 / 269 (23.79%)	47 / 252 (18.65%)
occurrences (all)	51	99	93

DRY MOUTH			
subjects affected / exposed	10 / 138 (7.25%)	18 / 269 (6.69%)	10 / 252 (3.97%)
occurrences (all)	11	19	12
NAUSEA			
subjects affected / exposed	29 / 138 (21.01%)	69 / 269 (25.65%)	60 / 252 (23.81%)
occurrences (all)	48	99	90
VOMITING			
subjects affected / exposed	21 / 138 (15.22%)	41 / 269 (15.24%)	36 / 252 (14.29%)
occurrences (all)	32	54	53
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	44 / 138 (31.88%)	66 / 269 (24.54%)	81 / 252 (32.14%)
occurrences (all)	75	94	117
DYSPNOEA			
subjects affected / exposed	42 / 138 (30.43%)	49 / 269 (18.22%)	69 / 252 (27.38%)
occurrences (all)	69	67	106
HAEMOPTYSIS			
subjects affected / exposed	11 / 138 (7.97%)	17 / 269 (6.32%)	15 / 252 (5.95%)
occurrences (all)	13	20	27
NASAL CONGESTION			
subjects affected / exposed	9 / 138 (6.52%)	4 / 269 (1.49%)	2 / 252 (0.79%)
occurrences (all)	12	4	2
PRODUCTIVE COUGH			
subjects affected / exposed	10 / 138 (7.25%)	23 / 269 (8.55%)	15 / 252 (5.95%)
occurrences (all)	17	26	24
Skin and subcutaneous tissue disorders			
DRY SKIN			
subjects affected / exposed	14 / 138 (10.14%)	19 / 269 (7.06%)	16 / 252 (6.35%)
occurrences (all)	16	20	20
HYPERHIDROSIS			
subjects affected / exposed	5 / 138 (3.62%)	17 / 269 (6.32%)	7 / 252 (2.78%)
occurrences (all)	5	19	10
PRURITUS			
subjects affected / exposed	20 / 138 (14.49%)	43 / 269 (15.99%)	36 / 252 (14.29%)
occurrences (all)	29	64	55
RASH			

subjects affected / exposed	21 / 138 (15.22%)	34 / 269 (12.64%)	29 / 252 (11.51%)
occurrences (all)	33	47	46
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	5 / 138 (3.62%)	18 / 269 (6.69%)	17 / 252 (6.75%)
occurrences (all)	5	23	19
DEPRESSION			
subjects affected / exposed	8 / 138 (5.80%)	12 / 269 (4.46%)	8 / 252 (3.17%)
occurrences (all)	9	14	10
INSOMNIA			
subjects affected / exposed	12 / 138 (8.70%)	20 / 269 (7.43%)	21 / 252 (8.33%)
occurrences (all)	12	23	25
Endocrine disorders			
HYPOTHYROIDISM			
subjects affected / exposed	8 / 138 (5.80%)	15 / 269 (5.58%)	10 / 252 (3.97%)
occurrences (all)	10	16	16
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	19 / 138 (13.77%)	41 / 269 (15.24%)	37 / 252 (14.68%)
occurrences (all)	29	70	58
BACK PAIN			
subjects affected / exposed	22 / 138 (15.94%)	35 / 269 (13.01%)	35 / 252 (13.89%)
occurrences (all)	28	51	46
MUSCLE SPASMS			
subjects affected / exposed	9 / 138 (6.52%)	10 / 269 (3.72%)	5 / 252 (1.98%)
occurrences (all)	10	11	5
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	9 / 138 (6.52%)	15 / 269 (5.58%)	14 / 252 (5.56%)
occurrences (all)	9	18	19
MUSCULOSKELETAL PAIN			
subjects affected / exposed	7 / 138 (5.07%)	23 / 269 (8.55%)	27 / 252 (10.71%)
occurrences (all)	8	25	41
MYALGIA			
subjects affected / exposed	7 / 138 (5.07%)	19 / 269 (7.06%)	16 / 252 (6.35%)
occurrences (all)	7	28	18
NECK PAIN			

subjects affected / exposed	10 / 138 (7.25%)	12 / 269 (4.46%)	14 / 252 (5.56%)
occurrences (all)	12	15	17
PAIN IN EXTREMITY			
subjects affected / exposed	15 / 138 (10.87%)	28 / 269 (10.41%)	25 / 252 (9.92%)
occurrences (all)	23	39	38
Infections and infestations			
LUNG INFECTION			
subjects affected / exposed	7 / 138 (5.07%)	3 / 269 (1.12%)	11 / 252 (4.37%)
occurrences (all)	7	3	13
NASOPHARYNGITIS			
subjects affected / exposed	14 / 138 (10.14%)	11 / 269 (4.09%)	18 / 252 (7.14%)
occurrences (all)	16	18	25
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	16 / 138 (11.59%)	26 / 269 (9.67%)	20 / 252 (7.94%)
occurrences (all)	18	45	27
URINARY TRACT INFECTION			
subjects affected / exposed	8 / 138 (5.80%)	18 / 269 (6.69%)	14 / 252 (5.56%)
occurrences (all)	14	29	19
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	34 / 138 (24.64%)	55 / 269 (20.45%)	74 / 252 (29.37%)
occurrences (all)	40	70	106
HYPOKALAEMIA			
subjects affected / exposed	11 / 138 (7.97%)	6 / 269 (2.23%)	9 / 252 (3.57%)
occurrences (all)	13	6	11

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 January 2014	Version 2
30 May 2014	Version 3
23 December 2014	Version 4
29 October 2015	Version 5
31 October 2016	Version 6

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28609226