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	

Results information

Result version number	v1
This version publication date	20 November 2018
First version publication date	01 July 2016

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	F. Hoffmann-La Roche AG, Roche Trial Information Hotline, +41 61 6878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, Roche Trial Information Hotline, +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	Interim
Date of interim/final analysis	28 May 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 May 2015
Global end of trial reached?	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)
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Protection of trial subjects:

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: -

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	
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	
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	
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	139	267	253
Completed	0	0	0
Not completed	139	267	253
On treatment	43	81	73
Consent withdrawn by subject	6	9	3
Physician decision	-	1	-
On survival follow-up	46	83	73
Death	36	87	100
Unknown reason	-	1	2
Lost to follow-up	1	1	2
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	139	267	253
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	66.7	62.4	63.6
standard deviation	± 10.4	± 10.2	± 9.3
Gender categorical Units: Subjects			
Female	68	103	100
Male	71	164	153

Reporting group values	Total		
Number of subjects	659		
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	- 		
Gender categorical Units: Subjects			
Female	271		
Male	388		

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	Cohorts 2 + 3
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This sub-group included participants from cohorts 2 and 3.

Subject analysis set title	Pharmacokinetic Evaluable Population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All participants who were treated and had evaluable pharmacokinetic samples were included in this group.

Primary: Percentage of Participants Achieving Objective Response (ORR) Per RECIST v1.1 as Assessed by IRF

End point title	Percentage of Participants Achieving Objective Response (ORR) Per RECIST v1.1 as Assessed by 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-PD non-target lesions and no new lesions. Results were reported by line of therapy and 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). Analyses of objective response rate was performed on efficacy evaluable population which included all treated participants who received any dose of atezolizumab during study treatment period. Number (n) equals (=) number of participants analyzed within the specified group

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	Cohort 2: Second Line Atezolizumab	Cohort 3: Third Line and Beyond Atezolizumab	Cohorts 2 + 3
Subject group type	Reporting group	Reporting group	Reporting group	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 to 38.5)	23.8 (16.5 to 32.3)	27 (19.1 to 36)	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)	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.pdf

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:

Objective response rate 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). The analyses of objective response was performed on the efficacy evaluable population; n = number of participants analyzed within the specified group.

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	Cohort 2: Second Line Atezolizumab	Cohort 3: Third Line and Beyond Atezolizumab	Cohorts 2 + 3
Subject group type	Reporting group	Reporting group	Reporting group	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)	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:

Objective response rate 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). The analyses of objective response was performed on the efficacy evaluable population; n= number of participants analyzed within the specified group.

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	Cohort 2: Second Line Atezolizumab	Cohort 3: Third Line and Beyond Atezolizumab	Cohorts 2 + 3
Subject group type	Reporting group	Reporting group	Reporting group	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 (11.1 to 31.8)	27 (19.4 to 35.8)	30.4 (22.2 to 39.7)	28.7 (23 to 34.9)
TC3 or IC2/3 Responders (n= 123, 247, 236, 483)	16.3 (10.2 to 24)	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)	21 (16.3 to 26.4)	19.8 (15 to 25.2)	20.4 (17 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. The analyses of DOR was performed on the efficacy evaluable population; n = number of participants analyzed within the specified group. 99999 = data not available.

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	Cohort 2: Second Line Atezolizumab	Cohort 3: Third Line and Beyond Atezolizumab	Cohorts 2 + 3
Subject group type	Reporting group	Reporting group	Reporting group	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)	99999 (5.8 to 99999)	99999 (4.9 to 99999)	7.2 (5.6 to 99999)	7.2 (5.7 to 99999)
TC3 or IC2/3 DOR (n = 26, 43, 43, 86)	8.5 (5.6 to 99999)	8.4 (6.9 to 99999)	8.4 (5.7 to 99999)	8.4 (6.9 to 99999)
TC2/3 or IC2/3 DOR(n= 27, 46. 44, 90)	8.5 (5.6 to 99999)	8.4 (6.9 to 99999)	8.4 (5.7 to 99999)	8.4 (6.9 to 99999)

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. The analyses of DOR was performed on the efficacy evaluable population; n = number of participants analyzed within the specified group. 99999 = data not available.

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	Cohort 2: Second Line Atezolizumab	Cohort 3: Third Line and Beyond Atezolizumab	Cohorts 2 + 3
Subject group type	Reporting group	Reporting group	Reporting group	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)	99999 (8.1 to 99999)	8.4 (6.4 to 99999)	99999 (7.4 to 99999)
TC3 or IC2/3 DOR (n = 30, 48, 45, 93)	8.5 (8.5 to 99999)	99999 (99999 to 99999)	8.3 (7 to 99999)	99999 (8.3 to 99999)
TC2/3 or IC2/3 DOR (n= 31, 50, 46, 96)	99999 (8.5 to 99999)	99999 (99999 to 99999)	8.3 (7 to 99999)	99999 (8.3 to 99999)

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. The analyses of DOR was performed on the efficacy evaluable population; n = number of participants analyzed within the specified group. 99999 = data not available.

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	Cohort 2: Second Line Atezolizumab	Cohort 3: Third Line and Beyond Atezolizumab	Cohorts 2 + 3
Subject group type	Reporting group	Reporting group	Reporting group	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)	99999 (4.4 to 99999)	99999 (8.1 to 99999)	99999 (7.4 to 99999)	99999 (8.1 to 99999)
TC3 or IC2/3 DOR (n= 20, 54, 49, 103)	99999 (99999 to 99999)	99999 (99999 to 99999)	99999 (7.4 to 99999)	99999 (99999 to 99999)
TC2/3 or IC2/3 DOR (n = 22, 56, 50, 106)	99999 (4.5 to 99999)	99999 (99999 to 99999)	99999 (7.4 to 99999)	99999 (99999 to 99999)

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. Progressive Disease (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. The analyses of PFS was performed on the efficacy evaluable population; n = number of participants analyzed within the specified group.

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	Cohort 2: Second Line Atezolizumab	Cohort 3: Third Line and Beyond Atezolizumab	Cohorts 2 + 3
Subject group type	Reporting group	Reporting group	Reporting group	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)	2.8 (2.7 to 4)	2.8 (2.7 to 3)

TC2/3 or IC2/3 PFS (n= 139, 267, 253, 520)	5.5 (3 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. The analyses of PFS was performed on the efficacy evaluable population; n = number of participants analyzed within the specified group. 99999 = data not available.

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	Cohort 2: Second Line Atezolizumab	Cohort 3: Third Line and Beyond Atezolizumab	Cohorts 2 + 3
Subject group type	Reporting group	Reporting group	Reporting group	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 99999)	4.1 (2.7 to 6.5)	4.2 (3 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 (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 (2.8 to 4.1)	3 (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. The analyses of PFS was performed on the efficacy evaluable population; n = number of participants analyzed within the specified group. 99999 = data not available.

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	Cohort 2: Second Line Atezolizumab	Cohort 3: Third Line and Beyond Atezolizumab	Cohorts 2 + 3
Subject group type	Reporting group	Reporting group	Reporting group	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 99999)	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)	4.5 (4 to 6)	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:

The analyses was performed on the efficacy evaluable populationn = number of participants analyzed within the specified group.

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	Cohort 2: Second Line Atezolizumab	Cohort 3: Third Line and Beyond Atezolizumab	Cohorts 2 + 3
Subject group type	Reporting group	Reporting group	Reporting group	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	68.8
TC3 or IC2/3 (n= 123, 247, 236, 483)	75.6	69.2	60.6	65
TC2/3 or IC2/3 (n= 139, 267, 253, 520)	74.1	67.4	60.5	64

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. The analyses was performed on the efficacy evaluable population; n = number of participants analyzed within the specified group. 99999 = data not available.

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	Cohort 2: Second Line Atezolizumab	Cohort 3: Third Line and Beyond Atezolizumab	Cohorts 2 + 3
Subject group type	Reporting group	Reporting group	Reporting group	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)	99999 (10.4 to 99999)	99999 (10.6 to 99999)	99999 (99999 to 99999)	99999 (12.1 to 99999)
TC3 or IC2/3 (n= 123, 247, 236, 483)	14 (14 to 99999)	99999 (12.1 to 99999)	99999 (8.4 to 99999)	99999 (12.1 to 99999)
TC2/3 or IC2/3 (n= 139, 267, 253, 520)	14 (14 to 99999)	99999 (11.2 to 99999)	99999 (8.4 to 99999)	99999 (11.2 to 99999)

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:

It is event-free rate (rate of survival) from the first dose of atezolizumab at 6 months. The analyses was performed on the efficacy evaluable population; n=number of participants analyzed within the specified group.

End point type	Secondary

End point timeframe:

Screening and 6 months

End point values	Cohort 1: First Line Atezolizumab	Cohort 2: Second Line Atezolizumab	Cohort 3: Third Line and Beyond Atezolizumab	Cohorts 2 + 3
Subject group type	Reporting group	Reporting group	Reporting group	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)	75.1 (67.1 to 83.1)	77.4 (72 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 (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 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:

The analyses was performed on the efficacy evaluable population; n = number of participants analyzed within the specified group.

End point type	Secondary

End point timeframe:

Screening and 12 months

End point values	Cohort 1: First Line Atezolizumab	Cohort 2: Second Line Atezolizumab	Cohort 3: Third Line and Beyond Atezolizumab	Cohorts 2 + 3
Subject group type	Reporting group	Reporting group	Reporting group	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 to 74)	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)	56.5 (50.6 to 62.5)
TC2/3 or IC2/3 (n=139, 267, 253, 520)	65 (54 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: Pertcentage of Participants Alive and Progression Free at 6 Months

End point title	PFS: Pertcentage 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. The analyses was performed on the efficacy evaluable population; n = number of participants analyzed within the specified group.

End point type	Secondary

End point timeframe:

Screening and 6 months

End point values	Cohort 1: First Line Atezolizumab	Cohort 2: Second Line Atezolizumab	Cohort 3: Third Line and Beyond Atezolizumab	Cohorts 2 + 3
Subject group type	Reporting group	Reporting group	Reporting group	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 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. The analyses was performed on the efficacy evaluable population; n = number of participants analyzed within the specified group.

End point type	Secondary

End point timeframe:

Screening and 12 months

End point values	Cohort 1: First Line Atezolizumab	Cohort 2: Second Line Atezolizumab	Cohort 3: Third Line and Beyond Atezolizumab	Cohorts 2 + 3
Subject group type	Reporting group	Reporting group	Reporting group	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 (13.1 to 45)	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 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:

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. The analyses were performed on the efficacy evaluable population. -9999 and 99999 = data not available.

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	Cohort 2: Second Line Atezolizumab	Cohort 3: Third Line and Beyond Atezolizumab	Cohorts 2 + 3
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	139	267	253	520
Units: months				
median (confidence interval 95%)	0.033 (-99999 to 99999)	0.033 (-99999 to 99999)	0.033 (-99999 to 99999)	0.033 (-99999 to 99999)

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:

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. The analyses were performed on the efficacy evaluable population. -99999 and 99999 = data not available.

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	Cohort 2: Second Line Atezolizumab	Cohort 3: Third Line and Beyond Atezolizumab	Cohorts 2 + 3
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	139	267	253	520
Units: months				
median (confidence interval 95%)	0.033 (-99999 to 99999)	0.033 (-99999 to 99999)	0.033 (-99999 to 99999)	0.033 (-99999 to 99999)

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:

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. The analyses were performed on the efficacy evaluable population. -99999 and 99999 = data not available.

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	Cohort 2: Second Line Atezolizumab	Cohort 3: Third Line and Beyond Atezolizumab	Cohorts 2 + 3
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	139	267	253	520
Units: months				
median (confidence interval 95%)	0.033 (-99999 to 99999)	0.033 (-99999 to 99999)	0.033 (-99999 to 99999)	0.033 (-99999 to 99999)

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. The analyses was performed on the efficacy evaluable population; n = number of participants analyzed for the specified time point.

End point type	Secondary

End point timeframe:

Pre-dose and 0.5 hours post dose on Cycle 1 Day 1, 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 (± 218)			
Cycle 1 Day 2 T=1 (n=47)	299 (± 65.3)			
Cycle 1 Day 4 T=3 (n=44)	220 (± 48.4)			
Cycle 1 Day 8 T=7 (n=38)	155 (± 35.4)			
Cycle 1 Day 15 T=14 (n=36)	106 (± 32.1)			
Cycle 1 Day 21 T=21 (n=596)	87.8 (± 41.7)			
Cycle 2 Day 21 T=42 (n=518)	134 (± 57.2)			
Cycle 3 Day 21 T=63 (n=467)	163 (± 70.7)			
Cycle 7 Day 21 T=147 (n=275)	212 (± 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 pharmocokinetics, safety and efficacy. The analyses was performed on the efficacy evaluable population; n = number of participants analyzed at the specified time point.

End point type	Secondary

End point timeframe:

Day 1 (± 2 Days for Cycles ≥ 2) and at treatment discontinuation visit (≤ 30 Days after last dose)

End point values	Cohort 1: First Line Atezolizumab	Cohort 2: Second Line Atezolizumab	Cohort 3: Third Line and Beyond Atezolizumab	Cohorts 2 + 3
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	135	257	247	504
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	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 5mm), appearance of new lesions, and/or unequivocal progression of non-target lesions. The analyses was performed on the efficacy evaluable population; n = number of participants analyzed within the specified group.

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	Cohort 2: Second Line Atezolizumab	Cohort 3: Third Line and Beyond Atezolizumab	Cohorts 2 + 3
Subject group type	Reporting group	Reporting group	Reporting group	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	73	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 5mm), appearance of new lesions, and/or unequivocal progression of non-target lesions.The analyses was performed on the efficacy evaluable population; n = number of participants analyzed within the specified group.

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	Cohort 2: Second Line Atezolizumab	Cohort 3: Third Line and Beyond Atezolizumab	Cohorts 2 + 3
Subject group type	Reporting group	Reporting group	Reporting group	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	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 5mm). The analyses was performed on the efficacy evaluable population; n = number of participants analyzed within the specified group.

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	Cohort 2: Second Line Atezolizumab	Cohort 3: Third Line and Beyond Atezolizumab	Cohorts 2 + 3
Subject group type	Reporting group	Reporting group	Reporting group	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	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 28 May 2015 (Up to 16 months)

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Cohort 1: First 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 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 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	43 / 139 (30.94%)	96 / 267 (35.96%)	94 / 253 (37.15%)
number of deaths (all causes)	36	87	100
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	0 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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

Glioblastoma multiforme			
subjects affected / exposed	0 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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 / 139 (0.00%)	0 / 267 (0.00%)	1 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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
Pericardial effusion malignant			
subjects affected / exposed	0 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			
subjects affected / exposed	0 / 139 (0.00%)	0 / 267 (0.00%)	1 / 253 (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 / 139 (0.72%)	1 / 267 (0.37%)	0 / 253 (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
Embolism			
subjects affected / exposed	1 / 139 (0.72%)	0 / 267 (0.00%)	0 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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
Hypotension			

subjects affected / exposed	1 / 139 (0.72%)	0 / 267 (0.00%)	0 / 253 (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 / 139 (0.00%)	0 / 267 (0.00%)	1 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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 / 139 (0.00%)	0 / 267 (0.00%)	1 / 253 (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 arterial occlusive disease			
subjects affected / exposed	1 / 139 (0.72%)	0 / 267 (0.00%)	0 / 253 (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
Superior vena cava syndrome			
subjects affected / exposed	0 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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 / 139 (0.72%)	1 / 267 (0.37%)	2 / 253 (0.79%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Chest pain			
subjects affected / exposed	0 / 139 (0.00%)	2 / 267 (0.75%)	2 / 253 (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 / 139 (0.00%)	0 / 267 (0.00%)	1 / 253 (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 / 139 (0.00%)	0 / 267 (0.00%)	1 / 253 (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
Fatigue			
subjects affected / exposed	0 / 139 (0.00%)	0 / 267 (0.00%)	1 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	2 / 253 (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
Hyperthermia			
subjects affected / exposed	0 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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
Influenza like illness			
subjects affected / exposed	0 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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 / 139 (0.00%)	2 / 267 (0.75%)	1 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	1 / 253 (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	0 / 139 (0.00%)	8 / 267 (3.00%)	7 / 253 (2.77%)
occurrences causally related to treatment / all	0 / 0	2 / 8	3 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	0 / 139 (0.00%)	1 / 267 (0.37%)	1 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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			
Bronchial haemorrhage			
subjects affected / exposed	0 / 139 (0.00%)	0 / 267 (0.00%)	1 / 253 (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 / 139 (0.00%)	0 / 267 (0.00%)	1 / 253 (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 / 139 (0.72%)	2 / 267 (0.75%)	2 / 253 (0.79%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	0 / 139 (0.00%)	1 / 267 (0.37%)	1 / 253 (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
Dyspnoea			
subjects affected / exposed	3 / 139 (2.16%)	4 / 267 (1.50%)	11 / 253 (4.35%)
occurrences causally related to treatment / all	0 / 3	2 / 5	0 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 139 (0.00%)	2 / 267 (0.75%)	4 / 253 (1.58%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	1 / 139 (0.72%)	0 / 267 (0.00%)	0 / 253 (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
Interstitial lung disease			
subjects affected / exposed	1 / 139 (0.72%)	0 / 267 (0.00%)	0 / 253 (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
Laryngeal haemorrhage			
subjects affected / exposed	0 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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	2 / 139 (1.44%)	1 / 267 (0.37%)	2 / 253 (0.79%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			

subjects affected / exposed	0 / 139 (0.00%)	1 / 267 (0.37%)	2 / 253 (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 / 139 (1.44%)	8 / 267 (3.00%)	5 / 253 (1.98%)
occurrences causally related to treatment / all	2 / 2	5 / 10	3 / 6
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 139 (0.00%)	0 / 267 (0.00%)	1 / 253 (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 / 139 (1.44%)	2 / 267 (0.75%)	1 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	1 / 253 (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 / 139 (0.00%)	0 / 267 (0.00%)	1 / 253 (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 / 139 (0.00%)	0 / 267 (0.00%)	2 / 253 (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
Respiratory failure			
subjects affected / exposed	1 / 139 (0.72%)	2 / 267 (0.75%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Tracheal stenosis			

subjects affected / exposed	0 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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	0 / 139 (0.00%)	2 / 267 (0.75%)	0 / 253 (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
Disorientation			
subjects affected / exposed	0 / 139 (0.00%)	2 / 267 (0.75%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	0 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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 / 139 (0.00%)	0 / 267 (0.00%)	1 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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	0 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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
Femur fracture			
subjects affected / exposed	1 / 139 (0.72%)	0 / 267 (0.00%)	0 / 253 (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
Incisional hernia			
subjects affected / exposed	0 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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 / 139 (0.00%)	2 / 267 (0.75%)	0 / 253 (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
Traumatic haemothorax			
subjects affected / exposed	1 / 139 (0.72%)	0 / 267 (0.00%)	0 / 253 (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
Congenital, familial and genetic disorders			
Tracheo-oesophageal fistula			
subjects affected / exposed	0 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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

Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 139 (0.00%)	1 / 267 (0.37%)	1 / 253 (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 / 1
Acute myocardial infarction			
subjects affected / exposed	1 / 139 (0.72%)	0 / 267 (0.00%)	0 / 253 (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 / 139 (0.00%)	0 / 267 (0.00%)	2 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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
Cardiac arrest			
subjects affected / exposed	0 / 139 (0.00%)	1 / 267 (0.37%)	1 / 253 (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 / 139 (0.00%)	0 / 267 (0.00%)	1 / 253 (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 tamponade			
subjects affected / exposed	1 / 139 (0.72%)	2 / 267 (0.75%)	0 / 253 (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
Cardiopulmonary failure			

subjects affected / exposed	0 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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
Coronary artery disease			
subjects affected / exposed	0 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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
Myocardial infarction			
subjects affected / exposed	1 / 139 (0.72%)	0 / 267 (0.00%)	0 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 139 (0.72%)	0 / 267 (0.00%)	0 / 253 (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
Cerebral infarction			
subjects affected / exposed	1 / 139 (0.72%)	0 / 267 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 139 (0.00%)	1 / 267 (0.37%)	3 / 253 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Dysarthria			
subjects affected / exposed	0 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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
Headache			

subjects affected / exposed	0 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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 / 139 (0.72%)	0 / 267 (0.00%)	0 / 253 (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 / 139 (0.72%)	0 / 267 (0.00%)	0 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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 / 139 (0.00%)	0 / 267 (0.00%)	1 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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
Subarachnoid haemorrhage			

subjects affected / exposed	1 / 139 (0.72%)	0 / 267 (0.00%)	0 / 253 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 139 (0.00%)	0 / 267 (0.00%)	1 / 253 (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
VIIth nerve paralysis			
subjects affected / exposed	1 / 139 (0.72%)	0 / 267 (0.00%)	0 / 253 (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
Vocal cord paralysis			
subjects affected / exposed	0 / 139 (0.00%)	0 / 267 (0.00%)	1 / 253 (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			
Anaemia			
subjects affected / exposed	0 / 139 (0.00%)	0 / 267 (0.00%)	3 / 253 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenitis			
subjects affected / exposed	1 / 139 (0.72%)	0 / 267 (0.00%)	0 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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 / 139 (0.72%)	0 / 267 (0.00%)	0 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	2 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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 / 139 (0.00%)	0 / 267 (0.00%)	1 / 253 (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 / 139 (0.72%)	1 / 267 (0.37%)	1 / 253 (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	1 / 139 (0.72%)	1 / 267 (0.37%)	0 / 253 (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
Diarrhoea			
subjects affected / exposed	2 / 139 (1.44%)	1 / 267 (0.37%)	2 / 253 (0.79%)
occurrences causally related to treatment / all	1 / 2	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 139 (0.00%)	1 / 267 (0.37%)	1 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 139 (0.00%)	2 / 267 (0.75%)	0 / 253 (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 / 139 (0.00%)	2 / 267 (0.75%)	0 / 253 (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 / 139 (0.72%)	3 / 267 (1.12%)	2 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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 / 139 (0.00%)	0 / 267 (0.00%)	1 / 253 (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 / 139 (0.72%)	0 / 267 (0.00%)	0 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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 / 139 (0.00%)	4 / 267 (1.50%)	3 / 253 (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 / 139 (0.72%)	0 / 267 (0.00%)	2 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	0 / 139 (0.00%)	1 / 267 (0.37%)	2 / 253 (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
Nephrolithiasis			
subjects affected / exposed	0 / 139 (0.00%)	0 / 267 (0.00%)	1 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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 / 139 (0.72%)	1 / 267 (0.37%)	0 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	1 / 253 (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	2 / 139 (1.44%)	1 / 267 (0.37%)	2 / 253 (0.79%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	0 / 139 (0.00%)	0 / 267 (0.00%)	2 / 253 (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
Intervertebral disc compression			
subjects affected / exposed	0 / 139 (0.00%)	0 / 267 (0.00%)	1 / 253 (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

Muscular weakness			
subjects affected / exposed	0 / 139 (0.00%)	1 / 267 (0.37%)	1 / 253 (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 chest pain			
subjects affected / exposed	0 / 139 (0.00%)	0 / 267 (0.00%)	1 / 253 (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
Pathological fracture			
subjects affected / exposed	0 / 139 (0.00%)	2 / 267 (0.75%)	0 / 253 (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
Spinal pain			
subjects affected / exposed	0 / 139 (0.00%)	0 / 267 (0.00%)	1 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	1 / 253 (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 / 139 (1.44%)	1 / 267 (0.37%)	0 / 253 (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
Bronchopneumonia			
subjects affected / exposed	1 / 139 (0.72%)	0 / 267 (0.00%)	0 / 253 (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
Catheter site infection			
subjects affected / exposed	0 / 139 (0.00%)	0 / 267 (0.00%)	1 / 253 (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 / 139 (0.72%)	0 / 267 (0.00%)	0 / 253 (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
Empyema			
subjects affected / exposed	1 / 139 (0.72%)	0 / 267 (0.00%)	0 / 253 (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 / 139 (0.72%)	0 / 267 (0.00%)	0 / 253 (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
Febrile infection			
subjects affected / exposed	0 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	2 / 253 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious colitis			
subjects affected / exposed	0 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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
Infectious pleural effusion			
subjects affected / exposed	1 / 139 (0.72%)	0 / 267 (0.00%)	0 / 253 (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 / 139 (0.72%)	0 / 267 (0.00%)	0 / 253 (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
Lobar pneumonia			
subjects affected / exposed	1 / 139 (0.72%)	0 / 267 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 139 (0.00%)	1 / 267 (0.37%)	1 / 253 (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
Lung abscess			
subjects affected / exposed	0 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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 / 139 (0.72%)	3 / 267 (1.12%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Osteomyelitis			
subjects affected / exposed	1 / 139 (0.72%)	0 / 267 (0.00%)	0 / 253 (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 / 139 (0.72%)	0 / 267 (0.00%)	0 / 253 (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	3 / 139 (2.16%)	7 / 267 (2.62%)	12 / 253 (4.74%)
occurrences causally related to treatment / all	0 / 3	0 / 9	1 / 12
deaths causally related to treatment / all	0 / 0	0 / 1	1 / 2
Pneumonia bacterial			

subjects affected / exposed	0 / 139 (0.00%)	0 / 267 (0.00%)	1 / 253 (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
Pyelonephritis			
subjects affected / exposed	0 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 139 (0.00%)	1 / 267 (0.37%)	1 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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 / 139 (0.72%)	0 / 267 (0.00%)	1 / 253 (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 / 139 (0.72%)	1 / 267 (0.37%)	2 / 253 (0.79%)
occurrences causally related to treatment / all	1 / 1	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vestibular neuronitis			
subjects affected / exposed	0 / 139 (0.00%)	0 / 267 (0.00%)	1 / 253 (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 / 139 (0.72%)	0 / 267 (0.00%)	0 / 253 (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 / 139 (0.00%)	0 / 267 (0.00%)	1 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	1 / 253 (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 / 139 (0.00%)	1 / 267 (0.37%)	0 / 253 (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 / 139 (0.00%)	5 / 267 (1.87%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	0 / 0	1 / 5	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 139 (0.00%)	2 / 267 (0.75%)	0 / 253 (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

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	115 / 139 (82.73%)	219 / 267 (82.02%)	224 / 253 (88.54%)
Investigations			
Weight decreased			

subjects affected / exposed	6 / 139 (4.32%)	17 / 267 (6.37%)	23 / 253 (9.09%)
occurrences (all)	6	20	29
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 139 (4.32%)	16 / 267 (5.99%)	20 / 253 (7.91%)
occurrences (all)	6	21	21
Headache			
subjects affected / exposed	12 / 139 (8.63%)	18 / 267 (6.74%)	28 / 253 (11.07%)
occurrences (all)	15	24	32
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	11 / 139 (7.91%)	22 / 267 (8.24%)	14 / 253 (5.53%)
occurrences (all)	16	41	27
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	12 / 139 (8.63%)	23 / 267 (8.61%)	33 / 253 (13.04%)
occurrences (all)	12	33	48
Chest pain			
subjects affected / exposed	5 / 139 (3.60%)	13 / 267 (4.87%)	21 / 253 (8.30%)
occurrences (all)	5	14	25
Chills			
subjects affected / exposed	4 / 139 (2.88%)	15 / 267 (5.62%)	14 / 253 (5.53%)
occurrences (all)	4	18	15
Fatigue			
subjects affected / exposed	45 / 139 (32.37%)	74 / 267 (27.72%)	83 / 253 (32.81%)
occurrences (all)	54	107	115
Influenza like illness			
subjects affected / exposed	11 / 139 (7.91%)	17 / 267 (6.37%)	13 / 253 (5.14%)
occurrences (all)	11	22	15
Malaise			
subjects affected / exposed	8 / 139 (5.76%)	6 / 267 (2.25%)	8 / 253 (3.16%)
occurrences (all)	9	7	8
Oedema peripheral			
subjects affected / exposed	5 / 139 (3.60%)	20 / 267 (7.49%)	18 / 253 (7.11%)
occurrences (all)	5	27	19
Pain			

subjects affected / exposed	10 / 139 (7.19%)	12 / 267 (4.49%)	8 / 253 (3.16%)
occurrences (all)	14	13	9
Pyrexia			
subjects affected / exposed	18 / 139 (12.95%)	38 / 267 (14.23%)	39 / 253 (15.42%)
occurrences (all)	20	54	46
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	8 / 139 (5.76%)	15 / 267 (5.62%)	15 / 253 (5.93%)
occurrences (all)	8	16	17
Constipation			
subjects affected / exposed	17 / 139 (12.23%)	35 / 267 (13.11%)	39 / 253 (15.42%)
occurrences (all)	20	41	48
Diarrhoea			
subjects affected / exposed	23 / 139 (16.55%)	50 / 267 (18.73%)	36 / 253 (14.23%)
occurrences (all)	29	67	57
Dry mouth			
subjects affected / exposed	8 / 139 (5.76%)	13 / 267 (4.87%)	10 / 253 (3.95%)
occurrences (all)	8	14	11
Nausea			
subjects affected / exposed	26 / 139 (18.71%)	59 / 267 (22.10%)	53 / 253 (20.95%)
occurrences (all)	37	77	70
Vomiting			
subjects affected / exposed	16 / 139 (11.51%)	34 / 267 (12.73%)	33 / 253 (13.04%)
occurrences (all)	19	44	39
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	33 / 139 (23.74%)	45 / 267 (16.85%)	66 / 253 (26.09%)
occurrences (all)	45	51	82
Dyspnoea			
subjects affected / exposed	34 / 139 (24.46%)	38 / 267 (14.23%)	56 / 253 (22.13%)
occurrences (all)	44	45	69
Haemoptysis			
subjects affected / exposed	9 / 139 (6.47%)	12 / 267 (4.49%)	9 / 253 (3.56%)
occurrences (all)	10	15	12
Nasal congestion			

subjects affected / exposed	7 / 139 (5.04%)	2 / 267 (0.75%)	2 / 253 (0.79%)
occurrences (all)	8	2	2
Productive cough			
subjects affected / exposed	6 / 139 (4.32%)	14 / 267 (5.24%)	9 / 253 (3.56%)
occurrences (all)	11	17	10
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	12 / 139 (8.63%)	15 / 267 (5.62%)	13 / 253 (5.14%)
occurrences (all)	12	15	13
Hyperhidrosis			
subjects affected / exposed	5 / 139 (3.60%)	15 / 267 (5.62%)	5 / 253 (1.98%)
occurrences (all)	5	16	7
Pruritus			
subjects affected / exposed	16 / 139 (11.51%)	31 / 267 (11.61%)	29 / 253 (11.46%)
occurrences (all)	20	40	39
Rash			
subjects affected / exposed	12 / 139 (8.63%)	27 / 267 (10.11%)	21 / 253 (8.30%)
occurrences (all)	19	37	28
Psychiatric disorders			
Anxiety			
subjects affected / exposed	4 / 139 (2.88%)	16 / 267 (5.99%)	12 / 253 (4.74%)
occurrences (all)	4	19	13
Insomnia			
subjects affected / exposed	9 / 139 (6.47%)	13 / 267 (4.87%)	16 / 253 (6.32%)
occurrences (all)	9	16	19
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	14 / 139 (10.07%)	30 / 267 (11.24%)	31 / 253 (12.25%)
occurrences (all)	24	47	39
Back pain			
subjects affected / exposed	15 / 139 (10.79%)	24 / 267 (8.99%)	27 / 253 (10.67%)
occurrences (all)	18	31	32
Musculoskeletal chest pain			
subjects affected / exposed	9 / 139 (6.47%)	12 / 267 (4.49%)	10 / 253 (3.95%)
occurrences (all)	9	13	12
Musculoskeletal pain			

subjects affected / exposed	6 / 139 (4.32%)	13 / 267 (4.87%)	24 / 253 (9.49%)
occurrences (all)	6	13	30
Myalgia			
subjects affected / exposed	2 / 139 (1.44%)	14 / 267 (5.24%)	13 / 253 (5.14%)
occurrences (all)	2	18	13
Pain in extremity			
subjects affected / exposed	11 / 139 (7.91%)	20 / 267 (7.49%)	14 / 253 (5.53%)
occurrences (all)	13	25	22
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	11 / 139 (7.91%)	5 / 267 (1.87%)	10 / 253 (3.95%)
occurrences (all)	12	5	11
Upper respiratory tract infection			
subjects affected / exposed	9 / 139 (6.47%)	14 / 267 (5.24%)	14 / 253 (5.53%)
occurrences (all)	9	17	15
Urinary tract infection			
subjects affected / exposed	3 / 139 (2.16%)	17 / 267 (6.37%)	9 / 253 (3.56%)
occurrences (all)	9	17	11
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	32 / 139 (23.02%)	47 / 267 (17.60%)	68 / 253 (26.88%)
occurrences (all)	35	55	81
Hypokalaemia			
subjects affected / exposed	10 / 139 (7.19%)	4 / 267 (1.50%)	9 / 253 (3.56%)
occurrences (all)	11	4	10

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 January 2014	The protocol was amended in response to the Voluntary Harmonisation Procedure (VHP), and the major clarifications were as follows: The description of eligible participants with locally advanced and metastatic non-small cell lung cancer in Cohort 1 in the inclusion criteria was further clarified. The exclusion criterion for participants with a positive Human Immunodeficiency Virus (HIV) test was updated. The timing of vital signs with the intravenous infusion of atezolizumab was clarified and made consistent throughout the protocol.
30 May 2014	Phase Ia study PCD4989g clinical data were updated. Inclusion criteria permitted participants with EGFR sensitizing mutations and anaplastic lymphoma kinase (ALK) translocations to be eligible for Cohort 1 after appropriate treatment and subsequent progression on an EGFR tyrosine kinase inhibitor or ALK inhibitor, respectively. Inclusion criteria regarding adequate hematologic and end organ function were revised as follows: the upper limit of 15,000 µL was removed from the white blood cell (WBC) count and creatinine clearance allowance was modified from greater than and equal to (≥) 50 to ≥ 30 milliliters per minute (mL/min). Treatment duration was modified to allow participants to be as long as they are experiencing clinical benefit; accordingly the 1-year initial treatment period, follow-up, and re-treatment periods no longer applied. The frequency of tumor assessments after 1 year of study treatment was increased from every 12 weeks to every 9 weeks. The total number of participants required for the study was increased from 300 to 635 to ensure a robust data set that allows for reliable evaluation of efficacy and safety, and to reflect the revision on the definition of positivity for PD-L1. In addition, the number of participants in each cohort was adjusted to reflect the new total number. The definition of positivity for PD-L1 was revised in Appendix 10 of the protocol to reflect the implementation introduced in the laboratory manual. The number of participants needed for Cohort 3 was clarified to require at least 75 participants with PD-L1 IHC 3. The plan to manage safety concerns was provided to reflect changes in the general guidelines. The Medical Monitor was changed.
23 December 2014	The Phase Ia Study PCD4989g clinical data were updated in the background section of the protocol. The description of eligible participants with positive PD-L1 was further clarified. The number of participants needed for Cohort 3 was updated to require approximately 100 participants with PD-L1 expression defined as TC3 or IC3 to support the primary efficacy analysis. The primary efficacy endpoint of ORR was revised to be analyzed by IRF assessment per RECIST v1.1. The INV-assessed ORR per modified RECIST would be analyzed as a secondary efficacy endpoint. The statistical plan was modified to reflect changes in the primary efficacy endpoint and the emerging information on subpopulations. The plan to manage safety concerns was revised to reflect changes in the general guidelines.
29 October 2015	The name of the test product, MPDL3280A, was changed to atezolizumab throughout the document. Additional/updated background information regarding previous and ongoing atezolizumab clinical studies was provided to align with Version 7 of the atezolizumab Investigator's Brochure (IB). The management of gastrointestinal, dermatologic, endocrine, pulmonary toxicity, hepatotoxicity, potential pancreatic or eye toxicity, and other immunemediated adverse events has been deleted from this protocol and reference was made to the atezolizumab IB. Systemic immune activation (SIA) has been identified as a potential risk of atezolizumab when given in combination with other immunomodulating agents. The management recommendations regarding early identification and management of SIA have been added. Clarifications have been made to the instructions for recording diagnosis versus signs and symptoms on the Adverse Event electronic case report form (eCRF).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The data was up to primary completion date.

Notes: