



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)

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 standard deviation | 66.7 ± 10.4 | 62.4 ± 10.2 | 63.6 ± 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 (\pm 3 days) for 12 months following Cycle 1, Day 1 and every 9 weeks (\pm 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 (\pm 3 days) for 12 months following Cycle 1, Day 1 and every 9 weeks (\pm 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.

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|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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|-----------------|--|
| 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: $\geq 30\%$ 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 (\pm 3 days) for 12 months following Cycle 1, Day 1 and every 9 weeks (\pm 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 (\pm 3 days) for 12 months following Cycle 1, Day 1 and every 9 weeks (\pm 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 (\pm 3 days) for 12 months following Cycle 1, Day 1 and every 9 weeks (\pm 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 (\pm 3 days) for 12 months following Cycle 1, Day 1 and every 9 weeks (\pm 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 (\pm 3 days) for 12 months following Cycle 1, Day 1 and every 9 weeks (\pm 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 (\pm 3 days) for 12 months following Cycle 1, Day 1 and every 9 weeks (\pm 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 (\pm 3 days) for 12 months following Cycle 1, Day 1 and every 9 weeks (\pm 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: Percentage of Participants Alive and Progression Free at 6 Months

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

End point description:

PD is defined as one or more of the following: at least 20% increase from nadir in the sum of diameters of target lesions (with an absolute increase of at least 5mm), appearance of new lesions, and/or unequivocal progression of non-target lesions. 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 (\pm 3 days) for 12 months following Cycle 1, Day 1 and every 9 weeks (\pm 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 (\pm 3 days) for 12 months following Cycle 1, Day 1 and every 9 weeks (\pm 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 (\pm 3 days) for 12 months following Cycle 1, Day 1 and every 9 weeks (\pm 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 pharmacokinetics, 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 (\pm 2 Days for Cycles \geq 2) and at treatment discontinuation visit (\leq 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 (\pm 3 days) for 12 months following Cycle 1, Day 1 and every 9 weeks (\pm 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 (\pm 3 days) for 12 months following Cycle 1, Day 1 and every 9 weeks (\pm 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 (\pm 3 days) for 12 months following Cycle 1, Day 1 and every 9 weeks (\pm 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 occurrences (all) | 6 / 139 (4.32%) 6 | 17 / 267 (6.37%) 20 | 23 / 253 (9.09%) 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 occurrences (all) | 10 / 139 (7.19%) 14 | 12 / 267 (4.49%) 13 | 8 / 253 (3.16%) 9 |
| Pyrexia subjects affected / exposed occurrences (all) | 18 / 139 (12.95%) 20 | 38 / 267 (14.23%) 54 | 39 / 253 (15.42%) 46 |
| Gastrointestinal disorders | | | |
| Abdominal pain subjects affected / exposed occurrences (all) | 8 / 139 (5.76%) 8 | 15 / 267 (5.62%) 16 | 15 / 253 (5.93%) 17 |
| Constipation subjects affected / exposed occurrences (all) | 17 / 139 (12.23%) 20 | 35 / 267 (13.11%) 41 | 39 / 253 (15.42%) 48 |
| Diarrhoea subjects affected / exposed occurrences (all) | 23 / 139 (16.55%) 29 | 50 / 267 (18.73%) 67 | 36 / 253 (14.23%) 57 |
| Dry mouth subjects affected / exposed occurrences (all) | 8 / 139 (5.76%) 8 | 13 / 267 (4.87%) 14 | 10 / 253 (3.95%) 11 |
| Nausea subjects affected / exposed occurrences (all) | 26 / 139 (18.71%) 37 | 59 / 267 (22.10%) 77 | 53 / 253 (20.95%) 70 |
| Vomiting subjects affected / exposed occurrences (all) | 16 / 139 (11.51%) 19 | 34 / 267 (12.73%) 44 | 33 / 253 (13.04%) 39 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough subjects affected / exposed occurrences (all) | 33 / 139 (23.74%) 45 | 45 / 267 (16.85%) 51 | 66 / 253 (26.09%) 82 |
| Dyspnoea subjects affected / exposed occurrences (all) | 34 / 139 (24.46%) 44 | 38 / 267 (14.23%) 45 | 56 / 253 (22.13%) 69 |
| Haemoptysis subjects affected / exposed occurrences (all) | 9 / 139 (6.47%) 10 | 12 / 267 (4.49%) 15 | 9 / 253 (3.56%) 12 |
| Nasal congestion | | | |

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

| | | | |
|---|-------------------------|-------------------------|-------------------------|
| subjects affected / exposed occurrences (all) | 6 / 139 (4.32%) 6 | 13 / 267 (4.87%) 13 | 24 / 253 (9.49%) 30 |
| Myalgia subjects affected / exposed occurrences (all) | 2 / 139 (1.44%) 2 | 14 / 267 (5.24%) 18 | 13 / 253 (5.14%) 13 |
| Pain in extremity subjects affected / exposed occurrences (all) | 11 / 139 (7.91%) 13 | 20 / 267 (7.49%) 25 | 14 / 253 (5.53%) 22 |
| Infections and infestations | | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 11 / 139 (7.91%) 12 | 5 / 267 (1.87%) 5 | 10 / 253 (3.95%) 11 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 9 / 139 (6.47%) 9 | 14 / 267 (5.24%) 17 | 14 / 253 (5.53%) 15 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 3 / 139 (2.16%) 9 | 17 / 267 (6.37%) 17 | 9 / 253 (3.56%) 11 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 32 / 139 (23.02%) 35 | 47 / 267 (17.60%) 55 | 68 / 253 (26.88%) 81 |
| Hypokalaemia subjects affected / exposed occurrences (all) | 10 / 139 (7.19%) 11 | 4 / 267 (1.50%) 4 | 9 / 253 (3.56%) 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 μ L was removed from the white blood cell (WBC) count and creatinine clearance allowance was modified from greater than and equal to (\geq) 50 to \geq 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: