



Clinical trial results:

A Phase III Multicenter, Randomized, Open-Label Study Evaluating the Efficacy and Safety of Atezolizumab (MPDL3280A, Anti-PD-L1 Antibody) in Combination With Carboplatin+Nab-Paclitaxel for Chemotherapy-Naive Patients With Stage IV Non-Squamous Non-Small Cell Lung Cancer

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2014-003206-32 |
| Trial protocol | DE BE IT FR ES |
| Global end of trial date | 18 January 2021 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v2 |
| This version publication date | 20 June 2021 |
| First version publication date | 29 March 2019 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | GO29537 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02367781 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | F. Hoffmann-La Roche AG |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4070 |
| Public contact | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com |
| Scientific contact | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 02 July 2020 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 18 January 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

This randomized Phase III, multicenter, open-label study was designed to evaluate the safety and efficacy of atezolizumab (an engineered anti-programmed death-ligand 1 [PD-L1] antibody) in combination with carboplatin+nab-paclitaxel compared with treatment with carboplatin+nab-paclitaxel in chemotherapy-naïve subjects with Stage IV non-squamous NSCLC.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 16 April 2015 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 57 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Israel: 35 |
| Country: Number of subjects enrolled | Belgium: 21 |
| Country: Number of subjects enrolled | Germany: 132 |
| Country: Number of subjects enrolled | Spain: 71 |
| Country: Number of subjects enrolled | France: 45 |
| Country: Number of subjects enrolled | Italy: 52 |
| Country: Number of subjects enrolled | Canada: 52 |
| Country: Number of subjects enrolled | United States: 315 |
| Worldwide total number of subjects | 723 |
| EEA total number of subjects | 321 |

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) | 362 |
| From 65 to 84 years | 358 |
| 85 years and over | 3 |

Subject disposition

Recruitment

Recruitment details:

At the time of study completion a few participants that were still on maintenance treatment with atezolizumab were moved to another study, Post-Trial Access Program, or commercial use. Therefore, the reason for discontinuation was entered "Study terminated by Sponsor" for these participants.

Pre-assignment

Screening details:

Participants in this study included: histologically or cytologically confirmed, Stage IV non-squamous NSCLC; and no prior treatment for Stage IV non-squamous NSCLC.

Period 1

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

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | Yes |
| Arm title | Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin) |

Arm description:

Participants received intravenous (IV) infusion of atezolizumab and carboplatin on Day 1 of each 21-day cycle, and nab-paclitaxel on Days 1, 8, and 15 of each 21-day cycle for 4 or 6 cycles or until loss of clinical benefit whichever occurred first during induction treatment phase. Participants received IV infusion of atezolizumab during maintenance treatment phase until loss of clinical benefit.

| | |
|--|---------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Atezolizumab |
| Investigational medicinal product code | |
| Other name | Tecentriq, MPDL3280A, RO5541267 |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Atezolizumab was administered as IV infusion at a dose of 1200 milligrams (mg) on Day 1 of each 21day cycle.

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

Dosage and administration details:

Nab-paclitaxel was administered as IV infusion at a dose of 100 milligrams per square meter (mg/m²) on Days 1, 8, and 15 of each 21-day cycle.

| | |
|--|-----------------|
| Investigational medicinal product name | Carboplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Carboplatin was administered at area under the concentration curve (AUC) 6 milligrams per milliliter per minute (mg/mL/min) on Day 1 of each 21-day cycle.

| | |
|------------------|------------------------------------|
| Arm title | Arm B (Nab-Paclitaxel+Carboplatin) |
|------------------|------------------------------------|

Arm description:

Participants received IV infusion of carboplatin on Day 1 and nab-paclitaxel on Days 1, 8, and 15 of each 21-day cycle for 4 or 6 cycles or until disease progression whichever occurs first during induction treatment phase. Participants received best supportive care during maintenance treatment phase. Switch maintenance to pemetrexed was also permitted. Participants who were consented prior to approval of protocol Version 5 were given the option to cross over to receive atezolizumab as monotherapy until disease progression.

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Nab-Paclitaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Nab-paclitaxel was administered as IV infusion at a dose of 100 milligrams per square meter (mg/m²) on Days 1, 8, and 15 of each 21-day cycle.

| | |
|--|-----------------|
| Investigational medicinal product name | Carboplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Carboplatin was administered at area under the concentration curve (AUC) 6 milligrams per milliliter per minute (mg/mL/min) on Day 1 of each 21-day cycle.

| | |
|--|-----------------|
| Investigational medicinal product name | Pemetrexed |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Switch maintenance to pemetrexed can be administered within 6 weeks of Day 1 of the last induction cycle.

| Number of subjects in period 1 | Arm A (Atezolizumab+Nab- Paclitaxel+Carboplatin) | Arm B (Nab- Paclitaxel+Carboplatin) |
|---|---|--|
| Started | 483 | 240 |
| Completed | 0 | 0 |
| Not completed | 483 | 240 |
| Adverse event, serious fatal | 330 | 176 |
| Physician decision | 7 | - |
| Immunotherapy Paused, Continuing Follow-Up Planned | 1 | - |
| Patient Admitted to Hospital | 1 | - |
| Patient Moving to Roll-Over Study | 17 | 5 |
| Study Terminated by Sponsor | 3 | 1 |
| Administrative-Change Facility | 1 | - |
| Death Prior First Dose | 1 | - |

| | | |
|--|----|----|
| Prolonged Hospitalization | 1 | - |
| Consent withdrawn by subject | 20 | 13 |
| Non-Compliance | 1 | - |
| Sponsor Withdraw Patient in Survival Follow-Up | 78 | 29 |
| Sponsor Decision | 2 | - |
| Lost to follow-up | 1 | 2 |
| Patient Moved to Commercial Atezolizumab Use | 14 | 9 |
| Randomized in Error | 5 | 4 |
| Protocol deviation | - | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin) |
|-----------------------|---|

Reporting group description:

Participants received intravenous (IV) infusion of atezolizumab and carboplatin on Day 1 of each 21-day cycle, and nab-paclitaxel on Days 1, 8, and 15 of each 21-day cycle for 4 or 6 cycles or until loss of clinical benefit whichever occurred first during induction treatment phase. Participants received IV infusion of atezolizumab during maintenance treatment phase until loss of clinical benefit.

| | |
|-----------------------|------------------------------------|
| Reporting group title | Arm B (Nab-Paclitaxel+Carboplatin) |
|-----------------------|------------------------------------|

Reporting group description:

Participants received IV infusion of carboplatin on Day 1 and nab-paclitaxel on Days 1, 8, and 15 of each 21-day cycle for 4 or 6 cycles or until disease progression whichever occurs first during induction treatment phase. Participants received best supportive care during maintenance treatment phase. Switch maintenance to pemetrexed was also permitted. Participants who were consented prior to approval of protocol Version 5 were given the option to cross over to receive atezolizumab as monotherapy until disease progression.

| Reporting group values | Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin) | Arm B (Nab-Paclitaxel+Carboplatin) | Total |
|---|--|------------------------------------|-------|
| Number of subjects | 483 | 240 | 723 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 245 | 117 | 362 |
| From 65-84 years | 236 | 122 | 358 |
| 85 years and over | 2 | 1 | 3 |
| Age Continuous Units: Years | | | |
| arithmetic mean | 63.8 | 64.4 | - |
| standard deviation | ± 9.5 | ± 8.9 | - |
| Sex: Female, Male Units: Participants | | | |
| Female | 206 | 102 | 308 |
| Male | 277 | 138 | 415 |
| Race (NIH/OMB) Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 14 | 3 | 17 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 18 | 8 | 26 |
| White | 428 | 222 | 650 |
| More than one race | 2 | 0 | 2 |

| | | | |
|-------------------------|-----|-----|-----|
| Unknown or Not Reported | 21 | 7 | 28 |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 25 | 12 | 37 |
| Not Hispanic or Latino | 426 | 213 | 639 |
| Unknown or Not Reported | 32 | 15 | 47 |

End points

End points reporting groups

| | |
|-----------------------|---|
| Reporting group title | Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin) |
|-----------------------|---|

Reporting group description:

Participants received intravenous (IV) infusion of atezolizumab and carboplatin on Day 1 of each 21-day cycle, and nab-paclitaxel on Days 1, 8, and 15 of each 21-day cycle for 4 or 6 cycles or until loss of clinical benefit whichever occurred first during induction treatment phase. Participants received IV infusion of atezolizumab during maintenance treatment phase until loss of clinical benefit.

| | |
|-----------------------|------------------------------------|
| Reporting group title | Arm B (Nab-Paclitaxel+Carboplatin) |
|-----------------------|------------------------------------|

Reporting group description:

Participants received IV infusion of carboplatin on Day 1 and nab-paclitaxel on Days 1, 8, and 15 of each 21-day cycle for 4 or 6 cycles or until disease progression whichever occurs first during induction treatment phase. Participants received best supportive care during maintenance treatment phase. Switch maintenance to pemetrexed was also permitted. Participants who were consented prior to approval of protocol Version 5 were given the option to cross over to receive atezolizumab as monotherapy until disease progression.

| | |
|----------------------------|--|
| Subject analysis set title | Arm B (Nab-Paclitaxel+Carboplatin Crossover) |
|----------------------------|--|

| | |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

Participants received IV infusion of carboplatin on Day 1 and nab-paclitaxel on Days 1, 8, and 15 of each 21-day cycle for 4 or 6 cycles or until disease progression whichever occurred first during induction treatment phase. Participants received best supportive care during maintenance treatment phase. Switch maintenance to pemetrexed was also permitted. Participants who were consented prior to approval of protocol Version 5 were given the option to cross over to receive atezolizumab as monotherapy until disease progression.

Primary: Progression-Free Survival (PFS) as Determined by the Investigator Using Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) in the ITT-WT Population

| | |
|-----------------|---|
| End point title | Progression-Free Survival (PFS) as Determined by the Investigator Using Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) in the ITT-WT Population |
|-----------------|---|

End point description:

PFS is defined as the time between the date of randomization and the date of first documented disease progression as determined by the investigator according to RECIST v1.1 or death from any cause, whichever occurs first in the ITT-WT population.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Up to approximately 35 months after first patient enrolled

| End point values | Arm A (Atezolizumab +Nab- Paclitaxel+Car boplatin) | Arm B (Nab- Paclitaxel+Car boplatin) | | |
|----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 456 | 229 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 7.0 (6.3 to 7.3) | 5.5 (4.4 to 5.9) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | PFS in ITT WT Population |
| Comparison groups | Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin) v Arm B (Nab-Paclitaxel+Carboplatin) |
| Number of subjects included in analysis | 685 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[1] |
| P-value | < 0.0001 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.639 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.536 |
| upper limit | 0.763 |

Notes:

[1] - Stratified Analysis

Primary: Overall Survival (OS) in the ITT-WT Population

| | |
|------------------------|--|
| End point title | Overall Survival (OS) in the ITT-WT Population |
| End point description: | OS is defined as the time between the date of randomization and date of death from any cause in the ITT-WT population. |
| End point type | Primary |
| End point timeframe: | Up to approximately 35 months after first patient enrolled |

| | | | | |
|----------------------------------|--|--|--|--|
| End point values | Arm A (Atezolizumab +Nab- Paclitaxel+Car boplatin) | Arm B (Nab- Paclitaxel+Car boplatin) | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 456 | 229 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 18.6 (15.8 to 21.2) | 13.9 (12.0 to 18.7) | | |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | OS in ITT-WT Population |
| Comparison groups | Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin) v Arm B (Nab-Paclitaxel+Carboplatin) |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 685 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[2] |
| P-value | = 0.0298 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.788 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.636 |
| upper limit | 0.977 |

Notes:

[2] - Stratified Analysis

Secondary: PFS as Determined by the Investigator Using Recist v1.1 in the ITT Population, PD-L1 Expression Population, and PD-L1 Expression WT Population

| | |
|-----------------|--|
| End point title | PFS as Determined by the Investigator Using Recist v1.1 in the ITT Population, PD-L1 Expression Population, and PD-L1 Expression WT Population |
|-----------------|--|

End point description:

PFS is defined as the time between the date of randomization and the date of first documented disease progression as determined by the investigator according to RECIST v1.1 or death from any cause, whichever occurs first. The ITT population was defined as all randomized participants, regardless of receipt of the assigned treatment. The PD-L1 expression population is defined as one of the following: PD-L1 IHC TC1/2/3 or IC1/2/3 population, defined as ITT participants with PD-L1 IHC TC1/2/3 or IC1/2/3 expression in baseline tumor tissue; PD-L1 IHC TC2/3 or IC2/3 population, defined as ITT participants with PD-L1 IHC TC2/3 or IC2/3 expression in baseline tumor tissue; PD-L1 IHC TC3 or IC3 population, defined as ITT participants with PD-L1 IHC TC3 or IC3 expression in baseline tumor tissue. The PD-L1 expression WT population is defined as the PD-L1 expression population excluding participants with an activating EGFR mutation or ALK translocation.

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

End point timeframe:

Up to approximately 35 months after first subject enrolled

| End point values | Arm A (Atezolizumab +Nab- Paclitaxel+Car boplatin) | Arm B (Nab- Paclitaxel+Car boplatin) | | |
|--|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 483 | 240 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| ITT (n=483, n=240) | 7.0 (6.3 to 7.3) | 5.6 (4.5 to 5.9) | | |
| TC1/2/3 or IC1/2/3 ITT (n=230, n=111) | 7.5 (7.0 to 9.1) | 5.7 (4.5 to 6.6) | | |
| TC1/2/3 or IC1/2/3-WT ITT (n=216, n=107) | 7.5 (7.0 to 9.0) | 5.9 (4.5 to 6.6) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | PFS in ITT Population |
| Comparison groups | Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin) v Arm B (Nab-Paclitaxel+Carboplatin) |
| Number of subjects included in analysis | 723 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[3] |
| P-value | < 0.0001 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.647 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.545 |
| upper limit | 0.768 |

Notes:

[3] - Stratified Analysis

| | |
|---|--|
| Statistical analysis title | PFS in TC1/2/3 or IC1/2/3-WT ITT Population |
| Comparison groups | Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin) v Arm B (Nab-Paclitaxel+Carboplatin) |
| Number of subjects included in analysis | 723 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[4] |
| P-value | < 0.0001 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.561 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.432 |
| upper limit | 0.728 |

Notes:

[4] - Unstratified Analysis

| | |
|---|--|
| Statistical analysis title | PFS in TC1/2/3 or IC1/2/3 ITT Population |
| Comparison groups | Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin) v Arm B (Nab-Paclitaxel+Carboplatin) |
| Number of subjects included in analysis | 723 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[5] |
| P-value | < 0.0001 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.549 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.425 |
| upper limit | 0.708 |

Notes:

[5] - Unstratified Analysis

Secondary: OS as Determined by the Investigator Using Recist v1.1 in the ITT Population

| | |
|-----------------|--|
| End point title | OS as Determined by the Investigator Using Recist v1.1 in the ITT Population |
|-----------------|--|

End point description:

OS is defined as the time between the date of randomization and date of death from any cause in the ITT population.

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

End point timeframe:

Up to approximately 41 months after first subject enrolled

| End point values | Arm A (Atezolizumab +Nab- Paclitaxel+Car boplatin) | Arm B (Nab- Paclitaxel+Car boplatin) | | |
|----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 483 | 240 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 17.0 (14.9 to 19.7) | 13.5 (11.9 to 17.7) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | OS in ITT Population |
| Comparison groups | Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin) v Arm B (Nab-Paclitaxel+Carboplatin) |
| Number of subjects included in analysis | 723 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[6] |
| P-value | = 0.0732 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.837 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.689 |
| upper limit | 1.017 |

Notes:

[6] - Stratified Analysis

Secondary: OS as Determined by the Investigator Using RECIST v1.1 in the PD-L1 Expression Population and PD-L1 Expression WT Population

| | |
|-----------------|---|
| End point title | OS as Determined by the Investigator Using RECIST v1.1 in the |
|-----------------|---|

End point description:

OS is defined as the time between the date of randomization and date of death from any cause in the PD-L1 Expression Population and PD-L1 Expression WT Population. The PD-L1 expression population is defined as one of the following: PD-L1 IHC TC1/2/3 or IC1/2/3 population, defined as ITT participants with PD-L1 IHC TC1/2/3 or IC1/2/3 expression in baseline tumor tissue; PD-L1 IHC TC2/3 or IC2/3 population, defined as ITT participants with PD-L1 IHC TC2/3 or IC2/3 expression in baseline tumor tissue; PD-L1 IHC TC3 or IC3 population, defined as ITT participants with PD-L1 IHC TC3 or IC3 expression in baseline tumor tissue. The PD-L1 expression WT population is defined as the PD-L1 expression population excluding participants with an activating EGFR mutation or ALK translocation.

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

End point timeframe:

Up to approximately 35 months after first patient enrolled

| End point values | Arm A (Atezolizumab +Nab- Paclitaxel+Car boplatin) | Arm B (Nab- Paclitaxel+Car boplatin) | | |
|---|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 230 | 111 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| TC1/2/3 or IC1/2/3 ITT (n=230, n=111) | 21.2 (17.3 to 28.2) | 16.9 (12.5 to 22.0) | | |
| TC1/2/3 or IC1/2/3 WT ITT (n=216, n=107) | 21.2 (18.1 to 28.2) | 16.9 (12.5 to 22.0) | | |

Statistical analyses

| Statistical analysis title | OS in TC1/2/3 or IC1/2/3 ITT Population |
|---|--|
| Comparison groups | Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin) v Arm B (Nab-Paclitaxel+Carboplatin) |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[7] |
| P-value | = 0.083 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.752 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.545 |
| upper limit | 1.039 |

Notes:

[7] - Unstratified Analysis

| Statistical analysis title | OS in TC1/2/3 or IC1/2/3 WT ITT Population |
|----------------------------|--|
|----------------------------|--|

| | |
|---|--|
| Comparison groups | Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin) v Arm B (Nab-Paclitaxel+Carboplatin) |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[8] |
| P-value | = 0.0813 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.746 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.536 |
| upper limit | 1.038 |

Notes:

[8] - Unstratified Analysis

Secondary: Percentage of Participants With an Objective Response (OR) (Complete Response [CR] or Partial Response [PR]) as Determined by the Investigator Using RECIST v1.1 in the ITT-WT Population

| | |
|-----------------|---|
| End point title | Percentage of Participants With an Objective Response (OR) (Complete Response [CR] or Partial Response [PR]) as Determined by the Investigator Using RECIST v1.1 in the ITT-WT Population |
|-----------------|---|

End point description:

ORR (confirmation not required) is defined as the proportion of participants with an objective response, either CR or PR, with the use of RECIST v1.1, as determined by the investigator in the ITT-WT population.

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

End point timeframe:

Up to approximately 41 months after first subject enrolled

| End point values | Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin) | Arm B (Nab-Paclitaxel+Carboplatin) | | |
|-----------------------------------|--|------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 452 | 227 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 60.2 | 41.0 | | |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | OR in ITT WT Population |
| Comparison groups | Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin) v Arm B (Nab-Paclitaxel+Carboplatin) |

| | |
|---|-----------------------------|
| Number of subjects included in analysis | 679 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[9] |
| P-value | < 0.0001 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Difference in Response Rate |
| Point estimate | 19.21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 11.05 |
| upper limit | 27.37 |

Notes:

[9] - Stratified Analysis

Secondary: Percentage of Participants With an Objective Response (OR) (Complete Response [CR] or Partial Response [PR]) as Determined by the Investigator Using RECIST v1.1 in the ITT Population, PD-L1 Expression Population, and PD-L1 Expression WT Population

| | |
|-----------------|---|
| End point title | Percentage of Participants With an Objective Response (OR) (Complete Response [CR] or Partial Response [PR]) as Determined by the Investigator Using RECIST v1.1 in the ITT Population, PD-L1 Expression Population, and PD-L1 Expression WT Population |
|-----------------|---|

End point description:

ORR (confirmation not required) is defined as proportion of participants with an objective response, either CR or PR, with the use of RECIST v1.1, as determined by investigator in ITT population, PD-L1 Expression population, and PD-L1 Expression WT population. ITT population was defined as all randomized participants, regardless of receipt of the assigned treatment. PD-L1 expression population is defined as one of the following: PD-L1 IHC TC1/2/3 or IC1/2/3 population, defined as ITT participants with PD-L1 IHC TC1/2/3 or IC1/2/3 expression in baseline tumor tissue; PD-L1 IHC TC2/3 or IC2/3 population, defined as ITT participants with PD-L1 IHC TC2/3 or IC2/3 expression in baseline tumor tissue; PD-L1 IHC TC3 or IC3 population, defined as ITT participants with PD-L1 IHC TC3 or IC3 expression in baseline tumor tissue. PD-L1 expression WT population is defined as PD-L1 expression population excluding participants with an activating EGFR mutation or ALK translocation.

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

End point timeframe:

Up to approximately 35 months after first subject enrolled

| End point values | Arm A (Atezolizumab +Nab- Paclitaxel+Car boplatin) | Arm B (Nab- Paclitaxel+Car boplatin) | | |
|--|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 479 | 237 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| ITT (n=479, n=237) | 59.1 | 42.2 | | |
| TC1/2/3 or IC1/2/3 ITT WT (n=215, n=106) | 65.6 | 46.2 | | |
| TC1/2/3 or IC1/2/3 ITT (n=229, n=109) | 64.6 | 45.0 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | OR in ITT Population |
| Comparison groups | Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin) v Arm B (Nab-Paclitaxel+Carboplatin) |
| Number of subjects included in analysis | 716 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[10] |
| P-value | < 0.0001 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Difference in Response Rate |
| Point estimate | 16.89 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 8.9 |
| upper limit | 24.88 |

Notes:

[10] - Stratified Analysis

| | |
|---|--|
| Statistical analysis title | OR in TC1/2/3 or IC1/2/3 ITT WT Population |
| Comparison groups | Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin) v Arm B (Nab-Paclitaxel+Carboplatin) |
| Number of subjects included in analysis | 716 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[11] |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.22 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.38 |
| upper limit | 3.56 |

Notes:

[11] - Stratified Analysis

| | |
|-----------------------------------|--|
| Statistical analysis title | OR in TC1/2/3 or IC1/2/3 ITT Population |
| Comparison groups | Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin) v Arm B (Nab-Paclitaxel+Carboplatin) |

| | |
|---|-----------------------------|
| Number of subjects included in analysis | 716 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[12] |
| P-value | = 0.0007 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.39 |
| upper limit | 3.51 |

Notes:

[12] - Stratified Analysis

Secondary: Duration of Response (DOR) as Determined by the Investigator Using RECIST v1.1 in ITT-WT Population, ITT Population, and PD-L1 Expression Population and PD-L1 Expression WT Population

| | |
|-----------------|---|
| End point title | Duration of Response (DOR) as Determined by the Investigator Using RECIST v1.1 in ITT-WT Population, ITT Population, and PD-L1 Expression Population and PD-L1 Expression WT Population |
|-----------------|---|

End point description:

DOR, defined for participants with objective response (OR) as time from 1st documented OR to documented disease progression as determined by investigator using RECIST v1.1, or death from any cause, whichever occurs 1st. ITT defined as all randomized participants, regardless of receipt of assigned treatment. ITT-WT defined as ITT population excluding participants with activating EGFR mutation or ALK translocation. PD-L1 expression population is defined as one of following: PD-L1 IHC TC1/2/3 or IC1/2/3 population, defined as ITT participants with PD-L1 IHC TC1/2/3 or IC1/2/3 expression in baseline tumor tissue; PD-L1 IHC TC2/3 or IC2/3 population, defined as ITT participants with PD-L1 IHC TC2/3 or IC2/3 expression in baseline tumor tissue; PD-L1 IHC TC3 or IC3 population, defined as ITT participants with PD-L1 IHC TC3 or IC3 expression in baseline tumor tissue. PD-L1 expression WT is defined as PD-L1 expression population excluding participants with activating EGFR mutation or ALK translocation.

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

End point timeframe:

Up to approximately 35 months after first subject enrolled

| End point values | Arm A (Atezolizumab +Nab- Paclitaxel+Car boplatin) | Arm B (Nab- Paclitaxel+Car boplatin) | | |
|---|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 283 | 100 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| ITT (n=283, n=100) | 6.2 (5.6 to 7.9) | 5.4 (4.1 to 5.8) | | |
| ITT-WT (n=267, n=93) | 6.7 (5.6 to 8.0) | 5.4 (3.9 to 5.8) | | |
| TC1/2/3 or IC1/2/3 ITT (n=148, n=49) | 7.2 (5.7 to 9.0) | 5.0 (3.2 to 6.1) | | |
| TC1/2/3 or IC1/2/3 ITT WT (n=141, n=49) | 7.2 (5.7 to 9.0) | 5.0 (3.2 to 6.1) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | DOR in ITT Population |
| Comparison groups | Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin) v Arm B (Nab-Paclitaxel+Carboplatin) |
| Number of subjects included in analysis | 383 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[13] |
| P-value | = 0.0002 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.614 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.473 |
| upper limit | 0.797 |

Notes:

[13] - Unstratified Analysis

| | |
|---|--|
| Statistical analysis title | DOR in ITT-WT Population |
| Comparison groups | Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin) v Arm B (Nab-Paclitaxel+Carboplatin) |
| Number of subjects included in analysis | 383 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[14] |
| P-value | = 0.0002 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.458 |
| upper limit | 0.785 |

Notes:

[14] - Unstratified Analysis

| | |
|-----------------------------------|--|
| Statistical analysis title | DOR in TC1/2/3 or IC1/2/3 ITT Population |
| Comparison groups | Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin) v Arm B (Nab-Paclitaxel+Carboplatin) |

| | |
|---|-----------------------------|
| Number of subjects included in analysis | 383 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[15] |
| P-value | = 0.0011 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.548 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.379 |
| upper limit | 0.791 |

Notes:

[15] - Unstratified Analysis

| | |
|---|--|
| Statistical analysis title | DOR in TC1/2/3 or IC1/2/3 ITT WT Population |
| Comparison groups | Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin) v Arm B (Nab-Paclitaxel+Carboplatin) |
| Number of subjects included in analysis | 383 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[16] |
| P-value | = 0.0014 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.551 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.381 |
| upper limit | 0.798 |

Notes:

[16] - Unstratified Analysis

Secondary: Percentage of Participants Who are Alive at Year 1 and 2 in ITT-WT Population and ITT Population

| | |
|--|--|
| End point title | Percentage of Participants Who are Alive at Year 1 and 2 in ITT-WT Population and ITT Population |
| End point description: The OS rate at the 1- and 2-year landmark time points after randomization. | |
| End point type | Secondary |
| End point timeframe: Up to 41 months after first patient enrolled | |

| End point values | Arm A (Atezolizumab +Nab- Paclitaxel+Car boplatin) | Arm B (Nab- Paclitaxel+Car boplatin) | | |
|-----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 483 | 240 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Alive at Year 1 ITT WT | 62.02 (57.53 to 66.51) | 54.56 (48.04 to 61.08) | | |
| Alive at Year 2 ITT WT | 40.43 (35.64 to 45.22) | 32.36 (25.80 to 38.92) | | |
| Alive at Year 1 ITT | 61.65 (57.29 to 66.02) | 54.47 (48.09 to 60.84) | | |
| Alive at Year 2 ITT | 39.73 (35.10 to 44.37) | 32.21 (25.79 to 38.63) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Alive at Year 1 ITT WT Population |
| Comparison groups | Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin) v Arm B (Nab-Paclitaxel+Carboplatin) |
| Number of subjects included in analysis | 723 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0647 |
| Method | Z-test |
| Parameter estimate | Difference in Event Free Rate |
| Point estimate | 7.46 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.45 |
| upper limit | 15.37 |

| | |
|---|--|
| Statistical analysis title | Alive at Year 2 ITT WT Population |
| Comparison groups | Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin) v Arm B (Nab-Paclitaxel+Carboplatin) |
| Number of subjects included in analysis | 723 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0516 |
| Method | Z-test |
| Parameter estimate | Difference in Event Free Rate |
| Point estimate | 8.07 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.06 |
| upper limit | 16.19 |

| | |
|---|--|
| Statistical analysis title | Alive at Year 1 ITT Population |
| Comparison groups | Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin) v Arm B (Nab-Paclitaxel+Carboplatin) |
| Number of subjects included in analysis | 723 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0683 |
| Method | Z-test |
| Parameter estimate | Difference in Event Free Rate |
| Point estimate | 7.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.54 |
| upper limit | 14.91 |

| | |
|---|--|
| Statistical analysis title | Alive at Year 2 ITT Population |
| Comparison groups | Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin) v Arm B (Nab-Paclitaxel+Carboplatin) |
| Number of subjects included in analysis | 723 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0625 |
| Method | Z-test |
| Parameter estimate | Difference in Event Free Rate |
| Point estimate | 7.53 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.39 |
| upper limit | 15.44 |

Secondary: Percentage of Participants Who are Alive at Year 1 and 2 in PD-L1 Expression Population and PD-L1 Expression WT Population

| | |
|-----------------|--|
| End point title | Percentage of Participants Who are Alive at Year 1 and 2 in PD-L1 Expression Population and PD-L1 Expression WT Population |
|-----------------|--|

End point description:

The OS rate at the 1- and 2-year landmark time points after randomization in the PD-L1 Expression Population and PD-L1 Expression WT Population. The PD-L1 expression population is defined as one of

the following: PD-L1 IHC TC1/2/3 or IC1/2/3 population, defined as ITT participants with PD-L1 IHC TC1/2/3 or IC1/2/3 expression in baseline tumor tissue; PD-L1 IHC TC2/3 or IC2/3 population, defined as ITT participants with PD-L1 IHC TC2/3 or IC2/3 expression in baseline tumor tissue; PD-L1 IHC TC3 or IC3 population, defined as ITT participants with PD-L1 IHC TC3 or IC3 expression in baseline tumor tissue. The PD-L1 expression WT population is defined as the PD-L1 expression population excluding participants with an activating EGFR mutation or ALK translocation.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to 35 months after first patient enrolled | |

| End point values | Arm A (Atezolizumab +Nab- Paclitaxel+Car- boplatin) | Arm B (Nab- Paclitaxel+Car- boplatin) | | |
|---|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 230 | 111 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Year 1 TC1/2/3 or IC1/2/3 ITT (n=230, n=111) | 68.56 (62.46 to 74.66) | 61.86 (52.55 to 71.17) | | |
| Year 2 TC1/2/3 or IC1/2/3 ITT(n=230, n=111) | 44.63 (35.99 to 53.27) | 35.98 (23.25 to 48.72) | | |
| Year 1 TC1/2/3 or IC1/2/3 ITT WT (n=216, n=107) | 68.84 (62.56 to 75.13) | 62.51 (53.07 to 71.94) | | |
| Year 2 TC1/2/3 or IC1/2/3 ITT WT (n=216, n=107) | 44.02 (34.86 to 53.18) | 35.33 (22.06 to 48.60) | | |

Statistical analyses

| Statistical analysis title | Alive at Year 1 TC1/2/3 or IC1/2/3 ITT |
|---|--|
| Comparison groups | Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin) v Arm B (Nab-Paclitaxel+Carboplatin) |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2385 |
| Method | Z-test |
| Parameter estimate | Difference in Event Free Rate |
| Point estimate | 6.69 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.44 |
| upper limit | 17.83 |

| Statistical analysis title | Alive at Year 2 TC1/2/3 or IC1/2/3 ITT |
|----------------------------|---|
| Comparison groups | Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin) v Arm B |

| | |
|---|-------------------------------|
| | (Nab-Paclitaxel+Carboplatin) |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.271 |
| Method | Z-test |
| Parameter estimate | Difference in Event Free Rate |
| Point estimate | 8.64 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.75 |
| upper limit | 24.03 |

| | |
|---|--|
| Statistical analysis title | Alive at Year 1 TC1/2/3 or IC1/2/3 ITT WT |
| Comparison groups | Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin) v Arm B (Nab-Paclitaxel+Carboplatin) |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2733 |
| Method | Z-test |
| Parameter estimate | Difference in Event Free Rate |
| Point estimate | 6.34 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5 |
| upper limit | 17.67 |

| | |
|---|--|
| Statistical analysis title | Alive at Year 2 TC1/2/3 or IC1/2/3 ITT WT |
| Comparison groups | Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin) v Arm B (Nab-Paclitaxel+Carboplatin) |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2909 |
| Method | Z-test |
| Parameter estimate | Difference in Event Free Rate |
| Point estimate | 8.69 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.44 |
| upper limit | 24.81 |

Secondary: Time to Deterioration (TTD) in Patient-Reported Lung Cancer Symptoms in the ITT-WT Population

| | |
|---|---|
| End point title | Time to Deterioration (TTD) in Patient-Reported Lung Cancer Symptoms in the ITT-WT Population |
| End point description: Defined as time from randomization to confirmed deterioration (10-point change) on the combined European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire–Core (EORTC QLQ-C30) and supplemental lung cancer module (EORTC QLQ-LC13) symptom subscales. | |
| End point type | Secondary |
| End point timeframe: Up to approximately 35 months after first subject enrolled | |

| End point values | Arm A (Atezolizumab +Nab- Paclitaxel+Car boplatin) | Arm B (Nab- Paclitaxel+Car boplatin) | | |
|----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 451 | 228 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 2.2 (1.8 to 3.1) | 1.9 (1.5 to 2.4) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | TTD in ITT WT Population |
| Comparison groups | Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin) v Arm B (Nab-Paclitaxel+Carboplatin) |
| Number of subjects included in analysis | 679 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[17] |
| P-value | = 0.3342 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.893 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.711 |
| upper limit | 1.123 |

Notes:

[17] - Stratified Analysis

Secondary: Change From Baseline in Patient-Reported Lung Cancer Symptoms Score Using the Symptoms in Lung Cancer (SILC) Scale

| | |
|-----------------|--|
| End point title | Change From Baseline in Patient-Reported Lung Cancer |
|-----------------|--|

End point description:

Change from baseline in patient-reported lung cancer symptoms (cough, dyspnea, and chest pain) on the symptom severity score of the Symptoms in Lung Cancer (SILC) scale. The SILC questionnaire comprises three individual symptoms (dyspnea, cough, chest pain) and will be scored at the individual symptom level, thus will have a dyspnea score, chest pain score, and cough score. Each individual symptom score will be calculated as the average of responses for the symptom items (e.g., Chest Pain Score = mean [item 1; item 2]). An increase in score is suggestive of a worsening in symptomology (i.e., frequency or severity). A score change of ≥ 0.3 points for the dyspnea and cough symptom scores is considered to be clinically significant; whereas a score change of ≥ 0.5 points for the chest pain score is considered to be clinically significant. Note: 999999=not available. FU=Follow-Up

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

End point timeframe:

Up to approximately 35 months after first subject enrolled

| End point values | Arm A (Atezolizumab +Nab- Paclitaxel+Car boplatin) | Arm B (Nab- Paclitaxel+Car boplatin) | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 236 | 129 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Chest Pain, Week 1 (n=203,n=114) | 0.19 (\pm 0.86) | 0.14 (\pm 0.90) | | |
| Chest Pain, Week 2 (n=204,n=108) | -0.02 (\pm 0.89) | 0.03 (\pm 0.91) | | |
| Chest Pain, Week 3 (n=197,n=106) | -0.05 (\pm 0.95) | 0.01 (\pm 0.92) | | |
| Chest Pain, Week 4 (n=190,n=102) | -0.11 (\pm 0.95) | 0.01 (\pm 1.02) | | |
| Chest Pain, Week 5 (n=192,n=97) | -0.12 (\pm 0.99) | 0.00 (\pm 1.03) | | |
| Chest Pain, Week 6 (n=182,n=98) | -0.24 (\pm 1.07) | 0.03 (\pm 1.03) | | |
| Chest Pain, Week 7 (n=176,n=87) | -0.23 (\pm 1.11) | 0.03 (\pm 1.08) | | |
| Chest Pain, Week 8 (n=169,n=80) | -0.21 (\pm 0.99) | -0.14 (\pm 1.00) | | |
| Chest Pain, Week 9 (n=172,n=80) | -0.18 (\pm 1.07) | -0.01 (\pm 1.07) | | |
| Chest Pain, Week 10 (n=160,n=75) | -0.10 (\pm 1.07) | -0.07 (\pm 1.01) | | |
| Chest Pain, Week 11 (n=171,n=78) | -0.11 (\pm 1.14) | 0.01 (\pm 0.96) | | |
| Chest Pain, Week 12 (n=160,n=72) | -0.15 (\pm 1.09) | -0.10 (\pm 1.13) | | |
| Chest Pain, Week 13 (n=151,n=61) | -0.26 (\pm 1.07) | -0.03 (\pm 1.02) | | |
| Chest Pain, Week 14 (n=144,n=62) | -0.28 (\pm 1.08) | -0.17 (\pm 1.18) | | |
| Chest Pain, Week 15 (n=143,n=51) | -0.26 (\pm 1.14) | -0.19 (\pm 1.19) | | |
| Chest Pain, Week 16 (n=139,n=52) | -0.33 (\pm 1.11) | -0.16 (\pm 1.20) | | |
| Chest Pain, Week 17 (n=145,n=53) | -0.33 (\pm 1.11) | -0.14 (\pm 1.13) | | |
| Chest Pain, Week 18 (n=136,n=49) | -0.28 (\pm 1.08) | -0.17 (\pm 1.13) | | |
| Chest Pain, Week 19 (n=124,n=45) | -0.28 (\pm 1.04) | -0.16 (\pm 1.00) | | |
| Chest Pain, Week 20 (n=123,n=43) | -0.26 (\pm 1.03) | -0.22 (\pm 1.02) | | |
| Chest Pain, Week 21 (n=126,n=41) | -0.25 (\pm 1.04) | -0.32 (\pm 1.08) | | |
| Chest Pain, Week 22 (n=116,n=37) | -0.28 (\pm 1.01) | -0.11 (\pm 1.03) | | |
| Chest Pain, Week 23 (n=122,n=35) | -0.24 (\pm 1.03) | -0.19 (\pm 1.04) | | |
| Chest Pain, Week 24 (n=110,n=34) | -0.21 (\pm 1.01) | -0.43 (\pm 1.03) | | |
| Chest Pain, Week 25 (n=104,n=31) | -0.20 (\pm 0.98) | -0.24 (\pm 1.07) | | |
| Chest Pain, Week 26 (n=109,n=31) | -0.17 (\pm 1.01) | -0.13 (\pm 0.91) | | |
| Chest Pain, Week 27 (n=102,n=27) | -0.22 (\pm 1.01) | -0.15 (\pm 1.17) | | |

| | | | | |
|----------------------------------|----------------|------------------|--|--|
| Chest Pain, Week 28 (n=96,n=28) | -0.20 (± 0.98) | -0.07 (± 0.91) | | |
| Chest Pain, Week 29 (n=104,n=27) | -0.27 (± 1.09) | -0.04 (± 0.92) | | |
| Chest Pain, Week 30 (n=100,n=23) | -0.15 (± 1.06) | -0.28 (± 1.12) | | |
| Chest Pain, Week 31 (n=93,n=25) | -0.16 (± 0.95) | -0.12 (± 1.05) | | |
| Chest Pain, Week 32 (n=88,n=25) | -0.19 (± 0.89) | -0.30 (± 1.10) | | |
| Chest Pain, Week 33 (n=88,n=25) | -0.18 (± 1.00) | -0.18 (± 1.11) | | |
| Chest Pain, Week 34 (n=85,n=24) | -0.18 (± 1.07) | -0.17 (± 1.18) | | |
| Chest Pain, Week 35 (n=87,n=20) | -0.10 (± 1.09) | 0.05 (± 1.06) | | |
| Chest Pain, Week 36 (n=85,n=20) | -0.21 (± 1.08) | -0.35 (± 1.01) | | |
| Chest Pain, Week 37 (n=82,n=21) | -0.18 (± 1.18) | -0.10 (± 1.04) | | |
| Chest Pain, Week 38 (n=83,n=19) | -0.32 (± 1.02) | -0.05 (± 1.01) | | |
| Chest Pain, Week 39 (n=78,n=18) | -0.28 (± 0.90) | -0.22 (± 1.06) | | |
| Chest Pain, Week 40 (n=76,n=14) | -0.19 (± 0.87) | -0.39 (± 0.81) | | |
| Chest Pain, Week 41 (n=77,n=16) | -0.25 (± 0.93) | -0.19 (± 0.89) | | |
| Chest Pain, Week 42 (n=70,n=16) | -0.16 (± 1.02) | -0.41 (± 0.74) | | |
| Chest Pain, Week 43 (n=68,n=16) | -0.24 (± 0.90) | -0.22 (± 0.95) | | |
| Chest Pain, Week 44 (n=76,n=16) | -0.24 (± 0.95) | 0.00 (± 0.98) | | |
| Chest Pain, Week 45 (n=69,n=14) | -0.14 (± 0.95) | -0.07 (± 0.78) | | |
| Chest Pain, Week 46 (n=71,n=15) | -0.15 (± 0.94) | -0.07 (± 1.03) | | |
| Chest Pain, Week 47 (n=70,n=13) | -0.22 (± 0.98) | -0.15 (± 0.90) | | |
| Chest Pain, Week 48 (n=66,n=11) | -0.14 (± 0.91) | -0.18 (± 0.98) | | |
| Chest Pain, Week 49 (n=65,n=9) | -0.22 (± 0.91) | -0.72 (± 0.75) | | |
| Chest Pain, Week 50 (n=70,n=8) | -0.18 (± 0.91) | -0.19 (± 0.70) | | |
| Chest Pain, Week 51 (n=65,n=10) | -0.13 (± 0.71) | -0.50 (± 0.78) | | |
| Chest Pain, Week 52 (n=72,n=7) | -0.15 (± 0.83) | -0.36 (± 0.63) | | |
| Chest Pain, Week 53 (n=64,n=6) | -0.20 (± 0.82) | -0.33 (± 0.61) | | |
| Chest Pain, Week 54 (n=65,n=7) | -0.22 (± 0.87) | -0.21 (± 0.70) | | |
| Chest Pain, Week 55 (n=62,n=5) | -0.34 (± 0.80) | -0.30 (± 0.76) | | |
| Chest Pain, Week 56 (n=62,n=6) | -0.19 (± 0.95) | -0.33 (± 0.68) | | |
| Chest Pain, Week 57 (n=62,n=5) | -0.19 (± 0.76) | -0.40 (± 0.65) | | |
| Chest Pain, Week 58 (n=56,n=4) | -0.32 (± 0.92) | -0.50 (± 1.15) | | |
| Chest Pain, Week 59 (n=52,n=4) | -0.25 (± 0.93) | -0.63 (± 0.75) | | |
| Chest Pain, Week 60 (n=48,n=4) | -0.27 (± 1.03) | -0.50 (± 1.08) | | |
| Chest Pain, Week 61 (n=49,n=5) | -0.28 (± 1.02) | -0.20 (± 1.15) | | |
| Chest Pain, Week 62 (n=41,n=5) | -0.16 (± 1.06) | -0.40 (± 1.47) | | |
| Chest Pain, Week 63 (n=43,n=5) | -0.12 (± 0.82) | -0.10 (± 1.34) | | |
| Chest Pain, Week 64 (n=42,n=4) | -0.15 (± 0.83) | 0.38 (± 1.44) | | |
| Chest Pain, Week 65 (n=40,n=3) | -0.31 (± 0.84) | 0.17 (± 1.76) | | |
| Chest Pain, Week 66 (n=38,n=4) | -0.25 (± 0.92) | 0.25 (± 1.19) | | |
| Chest Pain, Week 67 (n=33,n=4) | -0.18 (± 0.86) | 0.13 (± 1.44) | | |
| Chest Pain, Week 68 (n=34,n=4) | -0.15 (± 0.93) | -0.25 (± 1.55) | | |
| Chest Pain, Week 69 (n=35,n=3) | -0.13 (± 0.83) | -0.17 (± 1.89) | | |
| Chest Pain, Week 70 (n=36,n=3) | -0.14 (± 0.93) | 0.00 (± 1.80) | | |
| Chest Pain, Week 71 (n=31,n=3) | -0.10 (± 0.88) | 0.00 (± 0.87) | | |
| Chest Pain, Week 72 (n=29,n=2) | -0.24 (± 0.85) | -1.00 (± 0.71) | | |
| Chest Pain, Week 73 (n=28,n=1) | -0.25 (± 1.02) | -1.50 (± 999999) | | |
| Chest Pain, Week 74 (n=31,n=1) | -0.08 (± 0.93) | -1.50 (± 999999) | | |
| Chest Pain, Week 75 (n=31,n=1) | -0.21 (± 0.98) | -1.50 (± 999999) | | |
| Chest Pain, Week 76 (n=29,n=1) | 0.03 (± 1.00) | -1.50 (± 999999) | | |

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| Chest Pain, Week 77 (n=26,n=2) | -0.06 (± 0.89) | -1.50 (± 0.00) | | |
| Chest Pain, Week 78 (n=23,n=1) | -0.04 (± 0.84) | -1.50 (± 999999) | | |
| Chest Pain, Week 79 (n=19,n=1) | -0.11 (± 1.09) | -0.50 (± 999999) | | |
| Chest Pain, Week 80 (n=20,n=1) | -0.18 (± 1.05) | -1.50 (± 999999) | | |
| Chest Pain, Week 81 (n=17,n=1) | -0.59 (± 0.96) | -1.50 (± 999999) | | |
| Chest Pain, Week 82 (n=18,n=1) | -0.39 (± 0.96) | -1.50 (± 999999) | | |
| Chest Pain, Week 83 (n=22,n=1) | -0.34 (± 0.90) | -1.50 (± 999999) | | |
| Chest Pain, Week 84 (n=20,n=1) | -0.20 (± 0.75) | -1.50 (± 999999) | | |
| Chest Pain, Week 85 (n=17,n=1) | -0.44 (± 0.97) | -1.50 (± 999999) | | |
| Chest Pain, Week 86 (n=12,n=1) | -0.38 (± 0.64) | -1.50 (± 999999) | | |
| Chest Pain, Week 87 (n=15,n=1) | -0.53 (± 1.01) | -1.50 (± 999999) | | |
| Chest Pain, Week 88 (n=14,n=1) | -0.46 (± 1.06) | -1.50 (± 999999) | | |
| Chest Pain, Week 89 (n=11,n=1) | -0.55 (± 0.96) | -1.50 (± 999999) | | |
| Chest Pain, Week 90 (n=14,n=1) | -0.18 (± 0.85) | -1.50 (± 999999) | | |
| Chest Pain, Week 91 (n=11,n=1) | -0.32 (± 1.08) | -1.50 (± 999999) | | |
| Chest Pain, Week 92 (n=10,n=1) | -0.40 (± 0.66) | -1.50 (± 999999) | | |
| Chest Pain, Week 93 (n=11,n=1) | -0.18 (± 1.08) | -1.50 (± 999999) | | |
| Chest Pain, Week 94 (n=10,n=1) | -0.30 (± 1.09) | 999999 (± 999999) | | |
| Chest Pain, Week 95 (n=10,n=0) | -0.05 (± 1.26) | 999999 (± 999999) | | |
| Chest Pain, Week 96 (n=9,n=0) | -0.17 (± 1.25) | 999999 (± 999999) | | |
| Chest Pain, Week 97 (n=8,n=0) | -0.19 (± 1.31) | 999999 (± 999999) | | |
| Chest Pain, Week 98 (n=10,n=0) | -0.25 (± 1.16) | 999999 (± 999999) | | |
| Chest Pain, Week 99 (n=7,n=0) | -0.21 (± 1.47) | 999999 (± 999999) | | |
| Chest Pain, Week 100 (n=6,n=0) | -0.50 (± 1.38) | 999999 (± 999999) | | |
| Chest Pain, Week 101 (n=7,n=0) | -0.36 (± 1.38) | 999999 (± 999999) | | |
| Chest Pain, Week 102 (n=4,n=0) | -0.75 (± 1.71) | 999999 (± 999999) | | |
| Chest Pain, Week 103 (n=6,n=0) | -0.33 (± 1.54) | 999999 (± 999999) | | |
| Chest Pain, Week 104 (n=5,n=0) | -0.60 (± 1.39) | 999999 (± 999999) | | |
| Chest Pain, Week 105 (n=4,n=0) | -1.00 (± 1.41) | 999999 (± 999999) | | |
| Chest Pain, Week 106 (n=4,n=0) | -1.00 (± 1.41) | 999999 (± 999999) | | |
| Chest Pain, Week 107 (n=4,n=0) | -1.00 (± 1.41) | 999999 (± 999999) | | |

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| Chest Pain, Week 108 (n=4,n=0) | -0.75 (± 1.50) | 999999 (± 999999) | | |
| Chest Pain, Week 109 (n=5,n=0) | -0.60 (± 1.52) | 999999 (± 999999) | | |
| Chest Pain, Week 110 (n=6,n=0) | -0.42 (± 1.43) | 999999 (± 999999) | | |
| Chest Pain, Week 111 (n=5,n=0) | -0.50 (± 1.50) | 999999 (± 999999) | | |
| Chest Pain, Week 112 (n=4,n=0) | -0.13 (± 0.63) | 999999 (± 999999) | | |
| Chest Pain, Week 113 (n=4,n=0) | 0.13 (± 0.63) | 999999 (± 999999) | | |
| Chest Pain, Week 114 (n=3,n=0) | 0.00 (± 1.00) | 999999 (± 999999) | | |
| Chest Pain, Week 115 (n=2,n=0) | 0.25 (± 0.35) | 999999 (± 999999) | | |
| Chest Pain, Week 116 (n=2,n=0) | 0.50 (± 0.71) | 999999 (± 999999) | | |
| Chest Pain, Week 117 (n=2,n=0) | 0.25 (± 1.06) | 999999 (± 999999) | | |
| Chest Pain, Week 118 (n=2,n=0) | -0.25 (± 1.06) | 999999 (± 999999) | | |
| Chest Pain, Week 119 (n=2,n=0) | -0.25 (± 0.35) | 999999 (± 999999) | | |
| Chest Pain, Week 120 (n=2,n=0) | 0.00 (± 0.71) | 999999 (± 999999) | | |
| Chest Pain, Week 121 (n=2,n=0) | 0.00 (± 1.41) | 999999 (± 999999) | | |
| Chest Pain, Week 122 (n=2,n=0) | 0.00 (± 1.41) | 999999 (± 999999) | | |
| Chest Pain, Week 123 (n=2,n=0) | -0.75 (± 1.77) | 999999 (± 999999) | | |
| Chest Pain, Week 124 (n=1,n=0) | 0.50 (± 999999) | 999999 (± 999999) | | |
| Chest Pain, Week 125 (n=1,n=0) | 0.50 (± 999999) | 999999 (± 999999) | | |
| Chest Pain, Survival FU Month 1 (n=158, n=58) | 0.01 (± 1.13) | 0.22 (± 0.87) | | |
| Chest Pain, Survival FU Month 2 (n=42, n=47) | -0.07 (± 1.18) | -0.16 (± 0.96) | | |
| Chest Pain, Survival FU Month 3 (n=36, n=26) | 0.15 (± 1.33) | -0.08 (± 0.87) | | |
| Chest Pain, Survival FU Month 4 (n=23, n=28) | -0.28 (± 1.40) | -0.07 (± 0.79) | | |
| Chest Pain, Survival FU Month 5 (n=22, n=22) | -0.11 (± 1.49) | -0.02 (± 0.65) | | |
| Chest Pain, Survival FU Month 6 (n=15, n=21) | -0.37 (± 1.67) | 0.02 (± 0.78) | | |
| Cough, Week 1 (n=203, n=114) | 0.08 (± 0.69) | 0.04 (± 0.73) | | |
| Cough, Week 2 (n=204, n=108) | 0.02 (± 0.78) | 0.04 (± 0.84) | | |
| Cough, Week 3 (n=197, n=106) | 0.02 (± 0.86) | -0.09 (± 0.93) | | |
| Cough, Week 4 (n=190, n=102) | -0.06 (± 0.86) | -0.10 (± 0.93) | | |
| Cough, Week 5 (n=192, n=97) | -0.09 (± 0.84) | -0.09 (± 0.99) | | |
| Cough, Week 6 (n=182, n=98) | -0.15 (± 0.86) | -0.08 (± 0.98) | | |
| Cough, Week 7 (n=176, n=87) | -0.11 (± 0.86) | -0.06 (± 1.01) | | |
| Cough, Week 8 (n=169, n=80) | -0.13 (± 0.95) | -0.21 (± 1.04) | | |
| Cough, Week 9 (n=172, n=80) | -0.15 (± 0.99) | -0.13 (± 1.23) | | |
| Cough, Week 10 (n=166, n=75) | -0.20 (± 1.05) | -0.07 (± 1.17) | | |
| Cough, Week 11 (n=171, n=78) | -0.15 (± 1.03) | -0.15 (± 1.17) | | |
| Cough, Week 12 (n=160, n=72) | -0.17 (± 1.03) | -0.11 (± 1.09) | | |

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| Cough, Week 13 (n=151, n=61) | -0.24 (± 1.08) | -0.04 (± 1.11) | | |
| Cough, Week 14 (n=144, n=62) | -0.23 (± 1.06) | -0.18 (± 1.08) | | |
| Cough, Week 15 (n=143, n=51) | -0.27 (± 1.06) | -0.05 (± 1.10) | | |
| Cough, Week 16 (n=139, n=52) | -0.37 (± 1.07) | -0.25 (± 1.09) | | |
| Cough, Week 17 (n=145, n=53) | -0.32 (± 1.09) | -0.21 (± 1.01) | | |
| Cough, Week 18 (n=136, n=49) | -0.33 (± 1.07) | -0.33 (± 1.09) | | |
| Cough, Week 19 (n=124, n=45) | -0.33 (± 1.06) | -0.40 (± 0.89) | | |
| Cough, Week 20 (n=123, n=43) | -0.37 (± 1.10) | -0.31 (± 0.90) | | |
| Cough, Week 21 (n=126, n=41) | -0.37 (± 1.08) | -0.33 (± 0.96) | | |
| Cough, Week 22 (n=116, n=37) | -0.37 (± 1.15) | -0.24 (± 0.97) | | |
| Cough, Week 23 (n=122, n=35) | -0.30 (± 1.10) | -0.41 (± 1.03) | | |
| Cough, Week 24 (n=110, n=34) | -0.38 (± 1.09) | -0.54 (± 1.04) | | |
| Cough, Week 25 (n=104, n=31) | -0.49 (± 0.91) | -0.47 (± 1.05) | | |
| Cough, Week 26 (n=109, n=31) | -0.43 (± 0.99) | -0.34 (± 1.02) | | |
| Cough, Week 27 (n=102, n=27) | -0.41 (± 0.97) | -0.48 (± 0.98) | | |
| Cough, Week 28 (n=96, n=28) | -0.52 (± 0.96) | -0.43 (± 0.84) | | |
| Cough, Week 29 (n=104, n=27) | -0.43 (± 0.98) | -0.46 (± 0.91) | | |
| Cough, Week 30 (n=100, n=23) | -0.43 (± 0.95) | -0.46 (± 1.07) | | |
| Cough, Week 31 (n=93, n=25) | -0.32 (± 1.07) | -0.38 (± 0.77) | | |
| Cough, Week 32 (n=88, n=25) | -0.30 (± 0.94) | -0.12 (± 0.99) | | |
| Cough, Week 33 (n=88, n=25) | -0.19 (± 1.12) | -0.52 (± 1.03) | | |
| Cough, Week 34 (n=85, n=24) | -0.35 (± 1.12) | -0.33 (± 1.03) | | |
| Cough, Week 35 (n=87, n=20) | -0.46 (± 1.01) | 0.00 (± 1.22) | | |
| Cough, Week 36 (n=85, n=20) | -0.35 (± 1.08) | -0.20 (± 1.01) | | |
| Cough, Week 37 (n=82, n=21) | -0.46 (± 1.03) | -0.45 (± 1.11) | | |
| Cough, Week 38 (n=83, n=19) | -0.38 (± 1.06) | -0.03 (± 0.89) | | |
| Cough, Week 39 (n=78, n=18) | -0.27 (± 0.99) | -0.17 (± 1.00) | | |
| Cough, Week 40 (n=76, n=14) | -0.38 (± 0.95) | -0.50 (± 0.90) | | |
| Cough, Week 41 (n=77, n=16) | -0.44 (± 0.92) | -0.22 (± 0.77) | | |
| Cough, Week 42 (n=70, n=16) | -0.44 (± 0.92) | -0.41 (± 0.97) | | |
| Cough, Week 43 (n=68, n=16) | -0.39 (± 0.98) | -0.13 (± 0.92) | | |
| Cough, Week 44 (n=76, n=16) | -0.38 (± 0.94) | -0.16 (± 0.89) | | |
| Cough, Week 45 (n=69, n=14) | -0.30 (± 1.10) | -0.14 (± 1.03) | | |
| Cough, Week 46 (n=71, n=15) | -0.25 (± 0.99) | -0.03 (± 1.23) | | |
| Cough, Week 47 (n=70, n=13) | -0.44 (± 0.88) | -0.12 (± 1.23) | | |
| Cough, Week 48 (n=66, n=11) | -0.29 (± 0.99) | 0.14 (± 1.21) | | |
| Cough, Week 49 (n=65, n=9) | -0.38 (± 1.00) | -0.56 (± 1.36) | | |
| Cough, Week 50 (n=70, n=8) | -0.39 (± 0.96) | -0.19 (± 1.16) | | |
| Cough, Week 51 (n=65, n=10) | -0.30 (± 1.00) | -0.40 (± 1.20) | | |
| Cough, Week 52 (n=72, n=7) | -0.32 (± 1.03) | -0.21 (± 1.07) | | |
| Cough, Week 53 (n=64, n=6) | -0.37 (± 1.03) | -0.17 (± 1.33) | | |
| Cough, Week 54 (n=65, n=7) | -0.41 (± 0.93) | -0.07 (± 1.21) | | |
| Cough, Week 55 (n=62, n=5) | -0.40 (± 0.93) | 0.10 (± 1.34) | | |
| Cough, Week 56 (n=62, n=6) | -0.26 (± 0.94) | 0.17 (± 1.13) | | |
| Cough, Week 57 (n=62, n=5) | -0.35 (± 0.98) | 0.00 (± 1.27) | | |
| Cough, Week 58 (n=56, n=4) | -0.33 (± 1.06) | 0.13 (± 1.31) | | |
| Cough, Week 59 (n=52, n=4) | -0.31 (± 0.97) | 0.13 (± 1.60) | | |
| Cough, Week 60 (n=48, n=4) | -0.42 (± 0.89) | 0.38 (± 1.18) | | |
| Cough, Week 61 (n=49, n=5) | -0.35 (± 0.95) | 0.80 (± 1.20) | | |
| Cough, Week 62 (n=41, n=5) | -0.23 (± 1.03) | 0.50 (± 1.62) | | |
| Cough, Week 63 (n=43, n=5) | -0.22 (± 1.04) | 0.50 (± 1.27) | | |
| Cough, Week 64 (n=42, n=4) | -0.19 (± 1.07) | 0.00 (± 1.87) | | |

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| Cough, Week 65 (n=40, n=3) | -0.23 (± 1.04) | 0.83 (± 1.04) | | |
| Cough, Week 66 (n=38, n=4) | -0.29 (± 0.90) | 0.63 (± 1.03) | | |
| Cough, Week 67 (n=33, n=4) | -0.48 (± 0.91) | 0.38 (± 1.38) | | |
| Cough, Week 68 (n=34, n=4) | -0.34 (± 0.82) | 0.13 (± 1.49) | | |
| Cough, Week 69 (n=35, n=3) | -0.34 (± 1.03) | 0.17 (± 1.61) | | |
| Cough, Week 70 (n=36, n=3) | -0.26 (± 0.94) | 0.17 (± 1.61) | | |
| Cough, Week 71 (n=31, n=3) | -0.23 (± 0.91) | 0.33 (± 1.04) | | |
| Cough, Week 72 (n=29, n=2) | -0.48 (± 0.87) | -1.50 (± 1.41) | | |
| Cough, Week 73 (n=28, n=1) | -0.43 (± 0.91) | -0.50 (± 999999) | | |
| Cough, Week 74 (n=31, n=1) | -0.42 (± 0.93) | -0.50 (± 999999) | | |
| Cough, Week 75 (n=31, n=1) | -0.32 (± 1.00) | -0.50 (± 999999) | | |
| Cough, Week 76 (n=29, n=1) | -0.31 (± 0.91) | -0.50 (± 999999) | | |
| Cough, Week 77 (n=26, n=2) | -0.40 (± 0.92) | -0.50 (± 2.83) | | |
| Cough, Week 78 (n=23, n=1) | -0.52 (± 0.94) | 0.00 (± 999999) | | |
| Cough, Week 79 (n=19, n=1) | -0.08 (± 0.93) | 1.00 (± 999999) | | |
| Cough, Week 80 (n=20, n=1) | -0.48 (± 0.87) | 1.00 (± 999999) | | |
| Cough, Week 81 (n=17, n=1) | -0.44 (± 1.01) | -0.50 (± 999999) | | |
| Cough, Week 82 (n=18, n=1) | -0.39 (± 0.90) | 1.00 (± 999999) | | |
| Cough, Week 83 (n=22, n=1) | -0.25 (± 1.09) | 0.50 (± 999999) | | |
| Cough, Week 84 (n=20, n=1) | -0.30 (± 0.91) | 1.00 (± 999999) | | |
| Cough, Week 85 (n=17, n=1) | -0.32 (± 1.25) | 1.50 (± 999999) | | |
| Cough, Week 86 (n=12, n=1) | -0.54 (± 1.27) | 0.00 (± 999999) | | |
| Cough, Week 87 (n=15, n=1) | -0.33 (± 1.18) | 0.00 (± 999999) | | |
| Cough, Week 88 (n=14, n=1) | -0.46 (± 1.26) | 0.00 (± 999999) | | |
| Cough, Week 89 (n=11, n=1) | -0.36 (± 1.07) | 0.00 (± 999999) | | |
| Cough, Week 90 (n=14, n=1) | -0.29 (± 1.05) | 0.00 (± 999999) | | |
| Cough, Week 91 (n=11, n=1) | -0.27 (± 1.17) | 0.00 (± 999999) | | |
| Cough, Week 92 (n=10, n=1) | -0.35 (± 1.27) | 1.00 (± 999999) | | |
| Cough, Week 93 (n=11, n=1) | -0.55 (± 0.96) | 0.00 (± 999999) | | |
| Cough, Week 94 (n=10, n=0) | -0.40 (± 0.81) | 999999 (± 999999) | | |
| Cough, Week 95 (n=10, n=0) | 0.05 (± 1.23) | 999999 (± 999999) | | |
| Cough, Week 96 (n=9, n=0) | -0.28 (± 1.28) | 999999 (± 999999) | | |
| Cough, Week 97 (n=8, n=0) | -0.31 (± 1.19) | 999999 (± 999999) | | |
| Cough, Week 98 (n=10, n=0) | -0.10 (± 0.99) | 999999 (± 999999) | | |

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| Cough, Week 99 (n=7, n=0) | -0.43 (± 0.98) | 999999 (± 999999) | | |
| Cough, Week 100 (n=6, n=0) | -0.58 (± 0.86) | 999999 (± 999999) | | |
| Cough, Week 101 (n=7, n=0) | -0.50 (± 0.96) | 999999 (± 999999) | | |
| Cough, Week 102 (n=4, n=0) | -0.50 (± 0.41) | 999999 (± 999999) | | |
| Cough, Week 103 (n=6, n=0) | -0.75 (± 0.42) | 999999 (± 999999) | | |
| Cough, Week 104 (n=5, n=0) | -0.80 (± 0.27) | 999999 (± 999999) | | |
| Cough, Week 105 (n=4, n=0) | -0.63 (± 0.48) | 999999 (± 999999) | | |
| Cough, Week 106 (n=4, n=0) | -0.63 (± 0.48) | 999999 (± 999999) | | |
| Cough, Week 107 (n=4, n=0) | -0.63 (± 0.48) | 999999 (± 999999) | | |
| Cough, Week 108 (n=4, n=0) | -0.50 (± 0.71) | 999999 (± 999999) | | |
| Cough, Week 109 (n=5, n=0) | -0.50 (± 0.50) | 999999 (± 999999) | | |
| Cough, Week 110 (n=6, n=0) | -0.50 (± 0.45) | 999999 (± 999999) | | |
| Cough, Week 111 (n=5, n=0) | -0.30 (± 0.84) | 999999 (± 999999) | | |
| Cough, Week 112 (n=4, n=0) | -0.63 (± 0.48) | 999999 (± 999999) | | |
| Cough, Week 113 (n=4, n=0) | -0.25 (± 0.65) | 999999 (± 999999) | | |
| Cough, Week 114 (n=3, n=0) | -0.33 (± 0.29) | 999999 (± 999999) | | |
| Cough, Week 115 (n=2, n=0) | 0.25 (± 0.35) | 999999 (± 999999) | | |
| Cough, Week 116 (n=2, n=0) | -0.25 (± 1.06) | 999999 (± 999999) | | |
| Cough, Week 117 (n=2, n=0) | -0.50 (± 0.71) | 999999 (± 999999) | | |
| Cough, Week 118 (n=2, n=0) | -0.25 (± 0.35) | 999999 (± 999999) | | |
| Cough, Week 119 (n=2, n=0) | 0.00 (± 0.00) | 999999 (± 999999) | | |
| Cough, Week 120 (n=2, n=0) | -0.25 (± 0.35) | 999999 (± 999999) | | |
| Cough, Week 121 (n=2, n=0) | -0.50 (± 0.71) | 999999 (± 999999) | | |
| Cough, Week 122 (n=2, n=0) | -0.50 (± 0.71) | 999999 (± 999999) | | |
| Cough, Week 123 (n=2, n=0) | -0.75 (± 1.06) | 999999 (± 999999) | | |
| Cough, Week 124 (n=1, n=0) | 0.50 (± 999999) | 999999 (± 999999) | | |
| Cough, Week 125 (n=1, n=0) | 0.50 (± 999999) | 999999 (± 999999) | | |
| Cough, Survival Follow-Up Month 1 (n=158, n=58) | -0.21 (± 1.05) | -0.01 (± 0.96) | | |
| Cough, Survival Follow-Up Month 2 (n=42, n=47) | -0.07 (± 1.16) | -0.31 (± 1.18) | | |
| Cough, Survival Follow-Up Month 3 (n=36, n=26) | -0.14 (± 1.12) | -0.13 (± 1.32) | | |
| Cough, Survival Follow-Up Month 4 (n=23, n=28) | -0.39 (± 1.15) | -0.45 (± 1.17) | | |

| | | | | |
|---|----------------|----------------|--|--|
| Cough, Survival Follow-Up Month 5 (n=22, n=22) | -0.25 (± 1.44) | -0.27 (± 1.32) | | |
| Cough, Survival Follow-Up Month 6 (n=15, n=21) | -0.23 (± 1.53) | -0.29 (± 1.26) | | |
| Dyspnoea, Week 1 (n=203, n=114) | 0.13 (± 0.76) | 0.23 (± 0.79) | | |
| Dyspnoea, Week 2 (n=204, n=108) | 0.10 (± 0.68) | 0.31 (± 0.84) | | |
| Dyspnoea, Week 3 (n=197, n=106) | 0.22 (± 0.78) | 0.32 (± 0.76) | | |
| Dyspnoea, Week 4 (n=190, n=102) | 0.23 (± 0.80) | 0.45 (± 0.84) | | |
| Dyspnoea, Week 5 (n=192, n=97) | 0.26 (± 0.84) | 0.42 (± 0.92) | | |
| Dyspnoea, Week 6 (n=182, n=96) | 0.27 (± 0.92) | 0.51 (± 0.95) | | |
| Dyspnoea, Week 7 (n=176, n=87) | 0.29 (± 0.88) | 0.60 (± 1.00) | | |
| Dyspnoea, Week 8 (n=169, n=80) | 0.32 (± 0.97) | 0.53 (± 1.02) | | |
| Dyspnoea, Week 9 (n=172, n=80) | 0.38 (± 0.95) | 0.62 (± 1.07) | | |
| Dyspnoea, Week 10 (n=166, n=75) | 0.41 (± 1.04) | 0.75 (± 1.13) | | |
| Dyspnoea, Week 11 (n=171, n=78) | 0.50 (± 1.05) | 0.60 (± 1.06) | | |
| Dyspnoea, Week 12 (n=160, n=72) | 0.47 (± 1.07) | 0.74 (± 1.08) | | |
| Dyspnoea, Week 13 (n=151, n=61) | 0.32 (± 1.00) | 0.76 (± 1.00) | | |
| Dyspnoea, Week 14 (n=144, n=62) | 0.34 (± 0.99) | 0.61 (± 1.10) | | |
| Dyspnoea, Week 15 (n=143, n=51) | 0.29 (± 1.06) | 0.71 (± 1.02) | | |
| Dyspnoea, Week 16 (n=139, n=52) | 0.22 (± 0.99) | 0.67 (± 1.11) | | |
| Dyspnoea, Week 17 (n=145, n=53) | 0.28 (± 1.10) | 0.68 (± 1.03) | | |
| Dyspnoea, Week 18 (n=136, n=49) | 0.23 (± 1.02) | 0.62 (± 1.03) | | |
| Dyspnoea, Week 19 (n=124, n=45) | 0.26 (± 1.06) | 0.54 (± 0.95) | | |
| Dyspnoea, Week 20 (n=123, n=43) | 0.24 (± 1.02) | 0.54 (± 1.08) | | |
| Dyspnoea, Week 21 (n=126, n=41) | 0.26 (± 1.04) | 0.39 (± 1.05) | | |
| Dyspnoea, Week 22 (n=116, n=37) | 0.21 (± 0.94) | 0.41 (± 1.05) | | |
| Dyspnoea, Week 23 (n=122, n=35) | 0.18 (± 0.97) | 0.41 (± 1.06) | | |
| Dyspnoea, Week 24 (n=110, n=34) | 0.22 (± 0.93) | 0.31 (± 1.01) | | |
| Dyspnoea, Week 25 (n=104, n=31) | 0.21 (± 0.88) | 0.20 (± 0.91) | | |
| Dyspnoea, Week 26 (n=109, n=31) | 0.17 (± 0.89) | 0.30 (± 1.00) | | |
| Dyspnoea, Week 27 (n=102, n=27) | 0.20 (± 1.04) | 0.30 (± 0.92) | | |
| Dyspnoea, Week 28 (n=96, n=28) | 0.16 (± 0.94) | 0.22 (± 1.01) | | |
| Dyspnoea, Week 29 (n=104, n=27) | 0.16 (± 0.92) | 0.33 (± 0.98) | | |
| Dyspnoea, Week 30 (n=100, n=23) | 0.24 (± 1.04) | 0.27 (± 1.02) | | |
| Dyspnoea, Week 31 (n=93, n=25) | 0.12 (± 0.99) | 0.26 (± 1.04) | | |
| Dyspnoea, Week 32 (n=88, n=25) | 0.20 (± 0.95) | 0.38 (± 1.06) | | |
| Dyspnoea, Week 33 (n=88, n=25) | 0.18 (± 0.98) | 0.19 (± 1.14) | | |
| Dyspnoea, Week 34 (n=85, n=24) | 0.21 (± 1.06) | 0.30 (± 1.02) | | |
| Dyspnoea, Week 35 (n=87, n=20) | 0.22 (± 1.03) | 0.46 (± 0.96) | | |
| Dyspnoea, Week 36 (n=85, n=20) | 0.21 (± 1.09) | 0.34 (± 1.14) | | |
| Dyspnoea, Week 37 (n=82, n=21) | 0.16 (± 1.13) | 0.10 (± 1.07) | | |
| Dyspnoea, Week 38 (n=83, n=19) | 0.18 (± 1.07) | 0.51 (± 0.99) | | |
| Dyspnoea, Week 39 (n=78, n=18) | 0.31 (± 1.04) | 0.26 (± 0.83) | | |
| Dyspnoea, Week 40 (n=76, n=14) | 0.31 (± 0.99) | 0.04 (± 0.79) | | |
| Dyspnoea, Week 41 (n=77, n=16) | 0.24 (± 0.99) | 0.18 (± 0.85) | | |
| Dyspnoea, Week 42 (n=70, n=16) | 0.26 (± 1.03) | 0.08 (± 0.70) | | |
| Dyspnoea, Week 43 (n=68, n=16) | 0.17 (± 1.13) | 0.41 (± 0.91) | | |
| Dyspnoea, Week 44 (n=76, n=16) | 0.22 (± 1.06) | 0.29 (± 0.86) | | |
| Dyspnoea, Week 45 (n=69, n=14) | 0.26 (± 1.09) | 0.31 (± 0.90) | | |
| Dyspnoea, Week 46 (n=71, n=15) | 0.29 (± 0.99) | 0.47 (± 1.03) | | |
| Dyspnoea, Week 47 (n=70, n=13) | 0.20 (± 1.02) | 0.45 (± 0.85) | | |
| Dyspnoea, Week 48 (n=66, n=11) | 0.32 (± 1.00) | 0.29 (± 0.91) | | |

| | | | | |
|--------------------------------|----------------|------------------|--|--|
| Dyspnoea, Week 49 (n=65, n=9) | 0.24 (± 1.04) | 0.00 (± 1.30) | | |
| Dyspnoea, Week 50 (n=70, n=8) | 0.32 (± 0.98) | 0.43 (± 0.88) | | |
| Dyspnoea, Week 51 (n=65, n=10) | 0.24 (± 0.92) | 0.06 (± 1.04) | | |
| Dyspnoea, Week 52 (n=72, n=7) | 0.27 (± 0.95) | 0.29 (± 0.90) | | |
| Dyspnoea, Week 53 (n=64, n=6) | 0.24 (± 1.00) | 0.30 (± 0.85) | | |
| Dyspnoea, Week 54 (n=65, n=7) | 0.28 (± 0.89) | 0.40 (± 0.95) | | |
| Dyspnoea, Week 55 (n=62, n=5) | 0.26 (± 0.98) | 0.44 (± 1.02) | | |
| Dyspnoea, Week 56 (n=62, n=6) | 0.26 (± 0.97) | 0.53 (± 1.10) | | |
| Dyspnoea, Week 57 (n=62, n=5) | 0.37 (± 0.95) | 0.24 (± 1.08) | | |
| Dyspnoea, Week 58 (n=56, n=4) | 0.19 (± 1.01) | 0.35 (± 1.40) | | |
| Dyspnoea, Week 59 (n=52, n=4) | 0.32 (± 0.84) | 0.35 (± 1.40) | | |
| Dyspnoea, Week 60 (n=48, n=4) | 0.35 (± 0.99) | 0.50 (± 1.51) | | |
| Dyspnoea, Week 61 (n=49, n=5) | 0.33 (± 1.03) | 0.60 (± 1.40) | | |
| Dyspnoea, Week 62 (n=41, n=5) | 0.45 (± 0.99) | 0.72 (± 1.36) | | |
| Dyspnoea, Week 63 (n=43, n=5) | 0.44 (± 1.05) | 0.56 (± 1.35) | | |
| Dyspnoea, Week 64 (n=42, n=4) | 0.36 (± 0.98) | -0.50 (± 1.91) | | |
| Dyspnoea, Week 65 (n=40, n=3) | 0.27 (± 0.97) | 0.07 (± 1.68) | | |
| Dyspnoea, Week 66 (n=38, n=4) | 0.32 (± 1.11) | 0.50 (± 1.23) | | |
| Dyspnoea, Week 67 (n=33, n=4) | 0.28 (± 0.91) | 0.40 (± 1.36) | | |
| Dyspnoea, Week 68 (n=34, n=4) | 0.35 (± 0.96) | 0.40 (± 1.43) | | |
| Dyspnoea, Week 69 (n=35, n=3) | 0.44 (± 1.02) | 0.73 (± 1.55) | | |
| Dyspnoea, Week 70 (n=36, n=3) | 0.33 (± 0.97) | 0.73 (± 1.55) | | |
| Dyspnoea, Week 71 (n=31, n=3) | 0.50 (± 0.95) | 0.60 (± 1.51) | | |
| Dyspnoea, Week 72 (n=29, n=3) | 0.17 (± 0.95) | 0.60 (± 1.44) | | |
| Dyspnoea, Week 73 (n=28, n=2) | 0.41 (± 0.96) | -1.80 (± 1.13) | | |
| Dyspnoea, Week 74 (n=31, n=1) | 0.30 (± 1.00) | -1.00 (± 999999) | | |
| Dyspnoea, Week 75 (n=31, n=1) | 0.26 (± 0.89) | -1.00 (± 999999) | | |
| Dyspnoea, Week 76 (n=29, n=1) | 0.23 (± 0.89) | -1.00 (± 999999) | | |
| Dyspnoea, Week 77 (n=26, n=2) | 0.20 (± 0.97) | -1.50 (± 1.56) | | |
| Dyspnoea, Week 78 (n=23, n=1) | 0.31 (± 0.94) | -1.00 (± 999999) | | |
| Dyspnoea, Week 79 (n=19, n=1) | 0.32 (± 0.95) | -1.00 (± 999999) | | |
| Dyspnoea, Week 80 (n=20, n=1) | 0.30 (± 0.92) | -1.00 (± 999999) | | |
| Dyspnoea, Week 81 (n=17, n=1) | -0.12 (± 1.00) | -0.80 (± 999999) | | |
| Dyspnoea, Week 82 (n=18, n=1) | 0.02 (± 1.06) | -0.80 (± 999999) | | |
| Dyspnoea, Week 83 (n=22, n=1) | 0.13 (± 1.01) | -1.00 (± 999999) | | |
| Dyspnoea, Week 84 (n=20, n=1) | 0.19 (± 1.00) | -1.00 (± 999999) | | |
| Dyspnoea, Week 85 (n=17, n=1) | 0.05 (± 1.17) | -0.80 (± 999999) | | |
| Dyspnoea, Week 86 (n=12, n=1) | -0.07 (± 1.05) | -1.00 (± 999999) | | |
| Dyspnoea, Week 87 (n=15, n=1) | -0.11 (± 0.96) | -1.00 (± 999999) | | |
| Dyspnoea, Week 88 (n=14, n=1) | 0.06 (± 1.12) | -1.00 (± 999999) | | |
| Dyspnoea, Week 89 (n=11, n=1) | 0.09 (± 0.91) | -1.00 (± 999999) | | |

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| Dyspnoea, Week 90 (n=14, n=1) | 0.37 (± 0.83) | -1.00 (± 999999) | | |
| Dyspnoea, Week 91 (n=11, n=1) | 0.33 (± 1.11) | -1.00 (± 999999) | | |
| Dyspnoea, Week 92 (n=10, n=1) | 0.20 (± 1.05) | -0.80 (± 999999) | | |
| Dyspnoea, Week 93 (n=93, n=1) | 0.35 (± 0.96) | -0.80 (± 999999) | | |
| Dyspnoea, Week 94 (n=10, n=0) | 0.50 (± 0.93) | 999999 (± 999999) | | |
| Dyspnoea, Week 95 (n=10, n=0) | 0.48 (± 0.98) | 999999 (± 999999) | | |
| Dyspnoea, Week 96 (n=9, n=0) | 0.51 (± 1.09) | 999999 (± 999999) | | |
| Dyspnoea, Week 97 (n=8, n=0) | 0.33 (± 1.18) | 999999 (± 999999) | | |
| Dyspnoea, Week 98 (n=10, n=0) | 0.38 (± 1.05) | 999999 (± 999999) | | |
| Dyspnoea, Week 99 (n=7, n=0) | 0.11 (± 0.99) | 999999 (± 999999) | | |
| Dyspnoea, Week 100 (n=6, n=0) | 0.27 (± 1.11) | 999999 (± 999999) | | |
| Dyspnoea, Week 101 (n=7, n=0) | 0.20 (± 1.11) | 999999 (± 999999) | | |
| Dyspnoea, Week 102 (n=4, n=0) | 0.35 (± 1.06) | 999999 (± 999999) | | |
| Dyspnoea, Week 103 (n=6, n=0) | 0.47 (± 1.29) | 999999 (± 999999) | | |
| Dyspnoea, Week 104 (n=5, n=0) | 0.48 (± 1.22) | 999999 (± 999999) | | |
| Dyspnoea, Week 105 (n=4, n=0) | -0.20 (± 0.71) | 999999 (± 999999) | | |
| Dyspnoea, Week 106 (n=4, n=0) | -0.20 (± 0.99) | 999999 (± 999999) | | |
| Dyspnoea, Week 107 (n=4, n=0) | -0.30 (± 0.62) | 999999 (± 999999) | | |
| Dyspnoea, Week 108 (n=4, n=0) | -0.15 (± 0.98) | 999999 (± 999999) | | |
| Dyspnoea, Week 109 (n=5, n=0) | 0.16 (± 1.17) | 999999 (± 999999) | | |
| Dyspnoea, Week 110 (n=6, n=0) | 0.33 (± 1.00) | 999999 (± 999999) | | |
| Dyspnoea, Week 111 (n=5, n=0) | -0.04 (± 0.86) | 999999 (± 999999) | | |
| Dyspnoea, Week 112 (n=4, n=0) | 0.20 (± 0.43) | 999999 (± 999999) | | |
| Dyspnoea, Week 113 (n=4, n=0) | 0.20 (± 0.67) | 999999 (± 999999) | | |
| Dyspnoea, Week 114 (n=3, n=0) | 0.40 (± 0.72) | 999999999999 (± 999999) | | |
| Dyspnoea, Week 115 (n=2, n=0) | 0.80 (± 0.85) | 999999 (± 999999) | | |
| Dyspnoea, Week 116 (n=2, n=0) | 0.60 (± 0.57) | 999999 (± 999999) | | |
| Dyspnoea, Week 117 (n=2, n=0) | 0.30 (± 0.14) | 999999 (± 999999) | | |
| Dyspnoea, Week 118 (n=2, n=0) | 0.30 (± 0.42) | 999999 (± 999999) | | |
| Dyspnoea, Week 119 (n=2, n=0) | 0.50 (± 0.42) | 999999 (± 999999) | | |
| Dyspnoea, Week 120 (n=2, n=0) | 0.30 (± 0.42) | 999999 (± 999999) | | |

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|--|------------------|-------------------|--|--|
| Dyspnoea, Week 121 (n=2, n=0) | 0.60 (± 0.57) | 999999 (± 999999) | | |
| Dyspnoea, Week 122 (n=2, n=0) | 0.60 (± 0.00) | 999999 (± 999999) | | |
| Dyspnoea, Week 123 (n=2, n=0) | -0.20 (± 0.57) | 999999 (± 999999) | | |
| Dyspnoea, Week 124 (n=1, n=0) | -0.20 (± 999999) | 999999 (± 999999) | | |
| Dyspnoea, Week 125 (n=1, n=0) | 0.20 (± 999999) | 999999 (± 999999) | | |
| Dyspnoea, Survival Follow-Up Month 1 (n=158, n=58) | 0.41 (± 1.11) | 0.60 (± 1.14) | | |
| Dyspnoea, Survival Follow-Up Month 2 (n=42, n=47) | 0.36 (± 1.20) | 0.46 (± 1.22) | | |
| Dyspnoea, Survival Follow-Up Month 3 (n=36, n=26) | 0.27 (± 0.96) | 0.61 (± 1.19) | | |
| Dyspnoea, Survival Follow-Up Month 4 (n=23, n=28) | 0.02 (± 1.11) | 0.45 (± 0.88) | | |
| Dyspnoea, Survival Follow-Up Month 5 (n=22, n=22) | 0.13 (± 1.24) | 0.48 (± 1.00) | | |
| Dyspnoea, Survival Follow-Up Month 6 (n=15, n=21) | -0.09 (± 1.29) | 0.54 (± 0.97) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Adverse Events

| | |
|---|--|
| End point title | Percentage of Participants With Adverse Events |
| End point description: | |
| Percentage of participants with at least one adverse event. Adverse event onset date before cross over. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to approximately 69 months after first patient enrolled | |

| End point values | Arm A (Atezolizumab +Nab- Paclitaxel+Car boplatin) | Arm B (Nab- Paclitaxel+Car boplatin) | | |
|-----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 473 | 232 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 99.6 | 98.7 | | |

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Baseline prevalence and post-baseline incidence of anti-drug antibodies (ADA) to Atezolizumab in the Arm A (Atezolizumab + Carboplatin or Cisplatin + Pemetrexed) and Arm B Carboplatin+nab-paclitaxel Crossover Participants

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

End point timeframe:

Up to approximately 35 months after first subject enrolled

| End point values | Arm A (Atezolizumab +Nab- Paclitaxel+Car boplatin) | Arm B (Nab- Paclitaxel+Car boplatin) | | |
|-----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 451 | 85 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| Baseline (n=451, n=84) | 3.1 | 4.8 | | |
| Post-baseline (n=446, n=85) | 22.4 | 23.5 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Serum Concentration (Cmax) of Atezolizumab for Patients in Atezolizumab+Carboplatin+Nab-Paclitaxel Arm

| | |
|-----------------|---|
| End point title | Maximum Observed Serum Concentration (Cmax) of Atezolizumab for Patients in Atezolizumab+Carboplatin+Nab-Paclitaxel Arm ^[18] |
|-----------------|---|

End point description:

Predose samples will be collected on the same day of treatment administration. The infusion duration of atezolizumab will be of 30-60 minutes.

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

End point timeframe:

Cycle 1 Day 1 and Cycle 3 Day 1 (Cycle length = 21 days)

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis for this end point.

| | | | | |
|--------------------------------------|--|--|--|--|
| End point values | Arm A (Atezolizumab +Nab- Paclitaxel+Car boplatin) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 465 | | | |
| Units: mcg/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 Day 1 (n=446) | 392 (± 114) | | | |
| Cycle 3 Day 1 (n=356) | 454 (± 170) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Observed Serum Concentration (Cmin) of Atezolizumab Prior to Infusion in Atezolizumab+Carboplatin+Nab-Paclitaxel

| | |
|-----------------|--|
| End point title | Minimum Observed Serum Concentration (Cmin) of Atezolizumab Prior to Infusion in Atezolizumab+Carboplatin+Nab-Paclitaxel ^[19] |
|-----------------|--|

End point description:

Predose samples will be collected on the same day of treatment administration.

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

End point timeframe:

Cycle 1 Day 21, Cycle 2 Day 21, Cycle 3 Day 21, and Cycle 7 Day 21 (Cycle length = 21 days)

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis for this end point.

| | | | | |
|-------------------------------------|--|--|--|--|
| End point values | Arm A (Atezolizumab +Nab- Paclitaxel+Car boplatin) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 465 | | | |
| Units: mcg/mL | | | | |
| geometric mean (standard deviation) | | | | |
| Cycle 1 Day 21 (n=416) | 70.9 (± 35.1) | | | |
| Cycle 2 Day 21 (n=384) | 111 (± 52.2) | | | |
| Cycle 3 Day 21 (n=352) | 134 (± 57.8) | | | |
| Cycle 7 Day 21 (n=257) | 218 (± 93.7) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations of Carboplatin for Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin)

| | |
|-----------------|--|
| End point title | Plasma Concentrations of Carboplatin for Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin) ^[20] |
|-----------------|--|

End point description:

Note: 999999=non-reportable.

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

End point timeframe:

Predose (same day of treatment administration), 5-10 minutes before end of carboplatin infusion, 1 hour after carboplatin infusion (infusion duration=15 to 30 minutes) on Day 1 of Cycle 1 and 3 (1 Cycle=21 days) (up to approximately 35 months)

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis for this end point.

| | | | | |
|---|---|--|--|--|
| End point values | Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 29 | | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 Day 1 Pre-dose (n=29) | 999999 (± 999999) | | | |
| Cycle 1 Day 1 Before End of Infusion (n=23) | 20500 (± 7500) | | | |
| Cycle 1 Day 1 Post Infusion(n=29) | 11900 (± 3100) | | | |
| Cycle 3 Day 1 Pre-dose (n=23) | 169 (± 63.8) | | | |
| Cycle 3 Day 1 Before End of Infusion (n=16) | 15300 (± 6600) | | | |
| Cycle 3 Day 1 Post Infusion (n=18) | 11400 (± 3060) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations of Carboplatin for Arm B (Nab-Paclitaxel+Carboplatin CrossOver)

| | |
|-----------------|---|
| End point title | Plasma Concentrations of Carboplatin for Arm B (Nab-Paclitaxel+Carboplatin CrossOver) |
|-----------------|---|

End point description:

Note: 999999=non-reportable.

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

End point timeframe:

Predose (same day of treatment administration), 5-10 minutes before end of carboplatin infusion, 1 hour after carboplatin infusion (infusion duration=15 to 30 minutes) on Day 1 of Cycle 1 and 3 (1 Cycle=21 days) (up to approximately 35 months)

| End point values | Arm B (Nab-Paclitaxel+Carboplatin Crossover) | | | |
|---|--|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 19 | | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 Day 1 (Pre-dose) (n=19) | 999999 (± 999999) | | | |
| Cycle 1 Day 1 Before End of Infusion (n=18) | 17000 (± 5200) | | | |
| Cycle 1 Day 1 Post Infusion (n=18) | 12400 (± 3800) | | | |
| Cycle 3 Day 1 Pre-dose (n=16) | 160 (± 48.8) | | | |
| Cycle 3 Day 1 Before End of Infusion (n=14) | 17800 (± 7550) | | | |
| Cycle 3 Day 1 Post Infusion (n=15) | 13400 (± 6650) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations of Nab-Paclitaxel Reported as Total Paclitaxel for Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin)

| | |
|-----------------|--|
| End point title | Plasma Concentrations of Nab-Paclitaxel Reported as Total Paclitaxel for Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin) ^[21] |
|-----------------|--|

End point description:

Note: 999999=non-reportable.

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

End point timeframe:

Predose (same day of treatment administration), 5-10 minutes before end of nab-paclitaxel infusion, 1 hour after nab-paclitaxel infusion (infusion duration=30 minutes) on Day 1 of Cycle 1 and 3 (1 Cycle=21 days) (up to approximately 35 months)

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis for this end point.

| End point values | Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin) | | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 30 | | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |

| | | | | |
|---|-------------------|--|--|--|
| Cycle 1 Day 1 Pre-dose (n=29) | 999999 (± 999999) | | | |
| Cycle 1 Day 1 Before End of Infusion (n=27) | 3520 (± 2210) | | | |
| Cycle 1 Day 1 Post Infusion (n=25) | 307 (± 153) | | | |
| Cycle 3 Day 1 Pre-dose (n=23) | 999999 (± 999999) | | | |
| Cycle 3 Day 1 Before End of Infusion (n=17) | 4480 (± 3520) | | | |
| Cycle 3 Day 1 Post Infusion (n=18) | 357 (± 253) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations of Nab-Paclitaxel Reported as Total Paclitaxel for Arm B (Nab-Paclitaxel+Carboplatin Crossover)

| | |
|---|---|
| End point title | Plasma Concentrations of Nab-Paclitaxel Reported as Total Paclitaxel for Arm B (Nab-Paclitaxel+Carboplatin Crossover) |
| End point description: Note: 999999=non-reportable. | |
| End point type | Secondary |
| End point timeframe: Predose (same day of treatment administration), 5-10 minutes before end of nab-paclitaxel infusion, 1 hour after nab-paclitaxel infusion (infusion duration=30 minutes) on Day 1 of Cycle 1 and 3 (1 Cycle=21 days) (up to approximately 35 months) | |

| End point values | Arm B (Nab-Paclitaxel+Carboplatin Crossover) | | | |
|---|--|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 20 | | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 Day 1 Pre-dose (n=19) | 999999 (± 999999) | | | |
| Cycle 1 Day 1 Before End of Infusion (n=15) | 2530 (± 1420) | | | |
| Cycle 1 Day 1 Post Infusion (n=17) | 417 (± 217) | | | |
| Cycle 3 Day 1 Pre-dose (n=16) | 999999 (± 999999) | | | |
| Cycle 3 Day 1 Before End of Infusion (n=10) | 2030 (± 1690) | | | |
| Cycle 3 Day 1 Post Infusion (n=15) | 447 (± 322) | | | |

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first study drug to the data cutoff date: 18 January 2021 (approximately 69 months)

Adverse event reporting additional description:

Safety-evaluable population included all treated participants, defined as randomized participants who received any protocol treatment. For safety analyses, participants were grouped according to whether any full or partial dose of atezolizumab was received, including when atezolizumab was received in error.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 23.1 |

Reporting groups

| | |
|-----------------------|------------------------------------|
| Reporting group title | Arm B (Nab-Paclitaxel+Carboplatin) |
|-----------------------|------------------------------------|

Reporting group description:

Participants received IV infusion of carboplatin on Day 1 and nab-paclitaxel on Days 1, 8, and 15 of each 21-day cycle for 4 or 6 cycles or until disease progression whichever occurs first during induction treatment phase. Participants received best supportive care during maintenance treatment phase. Switch maintenance to pemetrexed was also permitted. Participants who were consented prior to approval of protocol Version 5 were given the option to cross over to receive atezolizumab as monotherapy until disease progression.

| | |
|-----------------------|---|
| Reporting group title | Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin) |
|-----------------------|---|

Reporting group description:

Participants received intravenous (IV) infusion of atezolizumab and carboplatin on Day 1 of each 21-day cycle, and nab-paclitaxel on Days 1, 8, and 15 of each 21-day cycle for 4 or 6 cycles or until loss of clinical benefit whichever occurred first during induction treatment phase. Participants received IV infusion of atezolizumab during maintenance treatment phase until loss of clinical benefit.

| Serious adverse events | Arm B (Nab-Paclitaxel+Carboplatin) | Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin) | |
|---|------------------------------------|---|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 87 / 232 (37.50%) | 252 / 473 (53.28%) | |
| number of deaths (all causes) | 178 | 338 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| TUMOUR PAIN | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ADENOCARCINOMA OF COLON | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NON-SMALL CELL LUNG CANCER | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| SARCOMA | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Vascular disorders | | | |
| ARTERIAL OCCLUSIVE DISEASE | | | |
| subjects affected / exposed | 2 / 232 (0.86%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DEEP VEIN THROMBOSIS | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 2 / 473 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| EMBOLISM | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 2 / 473 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FEMORAL ARTERY ANEURYSM | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPOTENSION | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 2 / 473 (0.42%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| JUGULAR VEIN THROMBOSIS | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PHLEBITIS | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| VASCULAR STENOSIS | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| ABORTION INDUCED | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| ASTHENIA | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 3 / 473 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CHEST PAIN | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 5 / 473 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DEATH | | | |
| subjects affected / exposed | 3 / 232 (1.29%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 3 | 1 / 1 | |
| DRUG INTERACTION | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| FATIGUE | | | |
| subjects affected / exposed | 2 / 232 (0.86%) | 2 / 473 (0.42%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GENERAL PHYSICAL HEALTH DETERIORATION | | | |
| subjects affected / exposed | 2 / 232 (0.86%) | 4 / 473 (0.85%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GENERALISED OEDEMA | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INFLUENZA LIKE ILLNESS | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 2 / 473 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MUCOSAL INFLAMMATION | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 2 / 473 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| OEDEMA PERIPHERAL | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 0 / 473 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PAIN | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 2 / 473 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PERFORMANCE STATUS DECREASED | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 2 / 473 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PYREXIA | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 232 (0.86%) | 8 / 473 (1.69%) | |
| occurrences causally related to treatment / all | 1 / 2 | 5 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SUDDEN DEATH | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 0 / 473 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| NON-CARDIAC CHEST PAIN | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 3 / 473 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SYSTEMIC INFLAMMATORY RESPONSE SYNDROME | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| ANAPHYLACTIC REACTION | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| VAGINAL HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| ACUTE RESPIRATORY FAILURE | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 3 / 473 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ASPIRATION | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| ASTHMA | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CHRONIC OBSTRUCTIVE PULMONARY DISEASE | | | |
| subjects affected / exposed | 5 / 232 (2.16%) | 13 / 473 (2.75%) | |
| occurrences causally related to treatment / all | 1 / 8 | 0 / 22 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| COUGH | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 2 / 473 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DYSPNOEA | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 12 / 473 (2.54%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 12 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| EPISTAXIS | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 0 / 473 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HAEMOPTYSIS | | | |
| subjects affected / exposed | 3 / 232 (1.29%) | 6 / 473 (1.27%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| LUNG DISORDER | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ORGANISING PNEUMONIA | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| OROPHARYNGEAL DISCOMFORT | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PLEURAL EFFUSION | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 8 / 473 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMONITIS | | | |
| subjects affected / exposed | 3 / 232 (1.29%) | 9 / 473 (1.90%) | |
| occurrences causally related to treatment / all | 1 / 3 | 9 / 9 | |
| deaths causally related to treatment / all | 0 / 1 | 2 / 2 | |
| PNEUMOTHORAX | | | |
| subjects affected / exposed | 2 / 232 (0.86%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMOTHORAX SPONTANEOUS | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 2 / 473 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PULMONARY EMBOLISM | | | |
| subjects affected / exposed | 5 / 232 (2.16%) | 17 / 473 (3.59%) | |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 18 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 6 | |
| PULMONARY HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 2 / 473 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RESPIRATORY DISTRESS | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| RESPIRATORY FAILURE | | | |
| subjects affected / exposed | 2 / 232 (0.86%) | 3 / 473 (0.63%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPOXIA | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INTERSTITIAL LUNG DISEASE | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Psychiatric disorders | | | |
| CONFUSIONAL STATE | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 2 / 473 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DISORIENTATION | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MENTAL STATUS CHANGES | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 4 / 473 (0.85%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| ALANINE AMINOTRANSFERASE INCREASED | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| ASPARTATE AMINOTRANSFERASE INCREASED | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 2 / 473 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BLOOD ALKALINE PHOSPHATASE INCREASED | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 2 / 473 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BLOOD CREATININE INCREASED | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BLOOD GLUCOSE INCREASED | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LYMPHOCYTE COUNT DECREASED | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NEUTROPHIL COUNT DECREASED | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 6 / 473 (1.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 6 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PLATELET COUNT DECREASED | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 2 / 473 (0.42%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| WHITE BLOOD CELL COUNT DECREASED | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 4 / 473 (0.85%) | |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| LIPASE INCREASED | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| FALL | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FEMORAL NECK FRACTURE | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 0 / 473 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FEMUR FRACTURE | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INFUSION RELATED REACTION | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 3 / 473 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SPINAL COMPRESSION FRACTURE | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 0 / 473 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SPINAL FRACTURE | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| UPPER LIMB FRACTURE | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 0 / 473 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| LUMBAR VERTEBRAL FRACTURE | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PELVIC FRACTURE | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| ACUTE MYOCARDIAL INFARCTION | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ANGINA UNSTABLE | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ATRIAL FIBRILLATION | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 4 / 473 (0.85%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ATRIAL FLUTTER | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 2 / 473 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BRADYCARDIA | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CARDIAC ANEURYSM | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 0 / 473 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CARDIAC ARREST | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 232 (0.00%) | 2 / 473 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| CARDIAC FAILURE | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CARDIAC FAILURE CHRONIC | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 0 / 473 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CARDIAC TAMPONADE | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 3 / 473 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MYOCARDIAL INFARCTION | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 3 / 473 (0.63%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 3 | |
| PALPITATIONS | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PERICARDIAL EFFUSION | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 6 / 473 (1.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SUPRAVENTRICULAR TACHYCARDIA | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 2 / 473 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| VENTRICULAR TACHYCARDIA | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| ACUTE CORONARY SYNDROME | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CARDIO-RESPIRATORY ARREST | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Nervous system disorders | | | |
| ATAXIA | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CAROTID ARTERY STENOSIS | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CEREBROVASCULAR ACCIDENT | | | |
| subjects affected / exposed | 2 / 232 (0.86%) | 4 / 473 (0.85%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DIZZINESS | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 2 / 473 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| EMBOLIC STROKE | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| EPILEPSY | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 232 (0.43%) | 2 / 473 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HEADACHE | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HEMIPARESIS | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 2 / 473 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ISCHAEMIC STROKE | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LETHARGY | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PARAESTHESIA | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SEIZURE | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 3 / 473 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SYNCOPE | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 3 / 473 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TOXIC NEUROPATHY | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| VASOGENIC CEREBRAL OEDEMA | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 0 / 473 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TRANSIENT ISCHAEMIC ATTACK | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| AGRANULOCYTOSIS | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 0 / 473 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ANAEMIA | | | |
| subjects affected / exposed | 8 / 232 (3.45%) | 14 / 473 (2.96%) | |
| occurrences causally related to treatment / all | 6 / 8 | 12 / 16 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FEBRILE NEUTROPENIA | | | |
| subjects affected / exposed | 5 / 232 (2.16%) | 9 / 473 (1.90%) | |
| occurrences causally related to treatment / all | 5 / 5 | 10 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HAEMOLYTIC URAEMIC SYNDROME | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LEUKOPENIA | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NEUTROPENIA | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 2 / 232 (0.86%) | 14 / 473 (2.96%) | |
| occurrences causally related to treatment / all | 2 / 2 | 16 / 16 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PANCYTOPENIA | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| THROMBOCYTOPENIA | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 6 / 473 (1.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 6 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| VERTIGO | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| ABDOMINAL PAIN | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 2 / 473 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ABDOMINAL PAIN LOWER | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ABDOMINAL PAIN UPPER | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COLITIS | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 2 / 473 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CONSTIPATION | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 1 / 232 (0.43%) | 3 / 473 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DIARRHOEA | | | |
| subjects affected / exposed | 2 / 232 (0.86%) | 14 / 473 (2.96%) | |
| occurrences causally related to treatment / all | 1 / 2 | 12 / 14 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DUODENAL ULCER | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTRITIS | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTROINTESTINAL HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 2 / 473 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTROINTESTINAL VASCULAR MALFORMATION HAEMORRHAGIC | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 0 / 473 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTROESOPHAGEAL REFLUX DISEASE | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ILEUS PARALYTIC | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 0 / 473 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LARGE INTESTINAL OBSTRUCTION | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LARGE INTESTINAL STENOSIS | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 0 / 473 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MELAENA | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NAUSEA | | | |
| subjects affected / exposed | 4 / 232 (1.72%) | 5 / 473 (1.06%) | |
| occurrences causally related to treatment / all | 3 / 5 | 4 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| OESOPHAGEAL FOOD IMPACTION | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SMALL INTESTINAL OBSTRUCTION | | | |
| subjects affected / exposed | 2 / 232 (0.86%) | 0 / 473 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| STOMATITIS | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| UPPER GASTROINTESTINAL HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| VOMITING | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 4 / 232 (1.72%) | 6 / 473 (1.27%) | |
| occurrences causally related to treatment / all | 3 / 5 | 4 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| IMMUNE-MEDIATED ENTEROCOLITIS | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 2 / 473 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| AUTOIMMUNE HEPATITIS | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 2 / 473 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BILE DUCT STONE | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CHOLECYSTITIS ACUTE | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CHOLESTASIS | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 2 / 473 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HEPATIC CIRRHOSIS | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| HEPATITIS | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HEPATOCELLULAR INJURY | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| IMMUNE-MEDIATED HEPATITIS | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| DRUG ERUPTION | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 0 / 473 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RASH | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SKIN ULCER | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| ACUTE KIDNEY INJURY | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 4 / 473 (0.85%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NEPHRITIS | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NEPHROLITHIASIS | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NEPHROPATHY TOXIC | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| POSTRENAL FAILURE | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RENAL FAILURE | | | |
| subjects affected / exposed | 2 / 232 (0.86%) | 5 / 473 (1.06%) | |
| occurrences causally related to treatment / all | 1 / 2 | 3 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TUBULOINTERSTITIAL NEPHRITIS | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| AUTOIMMUNE NEPHRITIS | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| URINARY RETENTION | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| HYPOTHYROIDISM | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 3 / 473 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ADDISON'S DISEASE | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GLUCOCORTICOID DEFICIENCY | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| ARTHRALGIA | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 2 / 473 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BACK PAIN | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 3 / 473 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BONE PAIN | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 2 / 473 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MUSCULAR WEAKNESS | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MUSCULOSKELETAL CHEST PAIN | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 2 / 473 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MYALGIA | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SPINAL PAIN | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LUMBAR SPINAL STENOSIS | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| APPENDICITIS PERFORATED | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ATYPICAL PNEUMONIA | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BACTERAEMIA | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BACTERIAL COLITIS | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BACTERIAL SEPSIS | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BRONCHITIS | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 6 / 473 (1.27%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CAMPYLOBACTER INFECTION | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CELLULITIS | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CLOSTRIDIUM DIFFICILE INFECTION | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CONJUNCTIVITIS | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CYSTITIS | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DEVICE RELATED INFECTION | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 2 / 473 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DIVERTICULITIS | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 0 / 473 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ENCEPHALITIS | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ERYSIPELAS | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FEBRILE INFECTION | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 232 (0.00%) | 3 / 473 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GANGRENE | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 0 / 473 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INFECTION | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 2 / 473 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INFECTIOUS PLEURAL EFFUSION | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INFLUENZA | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 5 / 473 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NASOPHARYNGITIS | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NEUTROPENIC INFECTION | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 0 / 473 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMONIA | | | |
| subjects affected / exposed | 15 / 232 (6.47%) | 45 / 473 (9.51%) | |
| occurrences causally related to treatment / all | 3 / 17 | 12 / 55 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 5 | |
| PULMONARY SEPSIS | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 3 / 473 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SEPSIS | | | |
| subjects affected / exposed | 2 / 232 (0.86%) | 7 / 473 (1.48%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 7 | |
| deaths causally related to treatment / all | 1 / 2 | 0 / 1 | |
| SEPTIC SHOCK | | | |
| subjects affected / exposed | 2 / 232 (0.86%) | 5 / 473 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 2 | 3 / 5 | |
| deaths causally related to treatment / all | 0 / 1 | 1 / 1 | |
| STAPHYLOCOCCAL SEPSIS | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| TRACHEOBRONCHITIS | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 3 / 473 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| URINARY TRACT INFECTION | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 4 / 473 (0.85%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| UROSEPSIS | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 232 (0.43%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| APPENDICITIS | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CLOSTRIDIUM DIFFICILE COLITIS | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 0 / 473 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CYTOMEGALOVIRUS COLITIS | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FURUNCLE | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PARAPHARYNGEAL SPACE INFECTION | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TOOTH INFECTION | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| VASCULAR DEVICE INFECTION | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| DECREASED APPETITE | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 232 (0.86%) | 0 / 473 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DEHYDRATION | | | |
| subjects affected / exposed | 2 / 232 (0.86%) | 3 / 473 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DIABETES MELLITUS | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DIABETIC KETOACIDOSIS | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| HYPERGLYCAEMIA | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPERKALAEMIA | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPOALBUMINAEMIA | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPOCALCAEMIA | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPOKALAEMIA | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 232 (0.86%) | 3 / 473 (0.63%) | |
| occurrences causally related to treatment / all | 1 / 2 | 2 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPOMAGNEAEMIA | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 1 / 473 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPONATRAEMIA | | | |
| subjects affected / exposed | 0 / 232 (0.00%) | 3 / 473 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TYPE 2 DIABETES MELLITUS | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 0 / 473 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Arm B (Nab-Paclitaxel+Carboplatin) | Arm A (Atezolizumab+Nab-Paclitaxel+Carboplatin) | |
|---|------------------------------------|---|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 227 / 232 (97.84%) | 467 / 473 (98.73%) | |
| Vascular disorders | | | |
| HYPOTENSION | | | |
| subjects affected / exposed | 13 / 232 (5.60%) | 34 / 473 (7.19%) | |
| occurrences (all) | 15 | 43 | |
| HYPERTENSION | | | |
| subjects affected / exposed | 8 / 232 (3.45%) | 26 / 473 (5.50%) | |
| occurrences (all) | 10 | 33 | |
| General disorders and administration site conditions | | | |
| ASTHENIA | | | |
| subjects affected / exposed | 40 / 232 (17.24%) | 89 / 473 (18.82%) | |
| occurrences (all) | 55 | 133 | |
| CHEST PAIN | | | |

| | | | |
|---|--------------------|--------------------|--|
| subjects affected / exposed | 12 / 232 (5.17%) | 33 / 473 (6.98%) | |
| occurrences (all) | 12 | 43 | |
| FATIGUE | | | |
| subjects affected / exposed | 109 / 232 (46.98%) | 228 / 473 (48.20%) | |
| occurrences (all) | 134 | 297 | |
| OEDEMA PERIPHERAL | | | |
| subjects affected / exposed | 25 / 232 (10.78%) | 71 / 473 (15.01%) | |
| occurrences (all) | 30 | 81 | |
| PAIN | | | |
| subjects affected / exposed | 8 / 232 (3.45%) | 30 / 473 (6.34%) | |
| occurrences (all) | 10 | 33 | |
| PYREXIA | | | |
| subjects affected / exposed | 22 / 232 (9.48%) | 80 / 473 (16.91%) | |
| occurrences (all) | 31 | 104 | |
| CHILLS | | | |
| subjects affected / exposed | 7 / 232 (3.02%) | 25 / 473 (5.29%) | |
| occurrences (all) | 8 | 32 | |
| MUCOSAL INFLAMMATION | | | |
| subjects affected / exposed | 8 / 232 (3.45%) | 24 / 473 (5.07%) | |
| occurrences (all) | 9 | 26 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| COUGH | | | |
| subjects affected / exposed | 39 / 232 (16.81%) | 135 / 473 (28.54%) | |
| occurrences (all) | 42 | 162 | |
| DYSPNOEA | | | |
| subjects affected / exposed | 51 / 232 (21.98%) | 134 / 473 (28.33%) | |
| occurrences (all) | 59 | 181 | |
| EPISTAXIS | | | |
| subjects affected / exposed | 27 / 232 (11.64%) | 69 / 473 (14.59%) | |
| occurrences (all) | 30 | 84 | |
| HAEMOPTYSIS | | | |
| subjects affected / exposed | 8 / 232 (3.45%) | 30 / 473 (6.34%) | |
| occurrences (all) | 8 | 42 | |
| PRODUCTIVE COUGH | | | |

| | | | |
|---|-------------------------|---------------------------|--|
| subjects affected / exposed occurrences (all) | 8 / 232 (3.45%) 8 | 35 / 473 (7.40%) 44 | |
| PNEUMONITIS subjects affected / exposed occurrences (all) | 0 / 232 (0.00%) 0 | 24 / 473 (5.07%) 26 | |
| Psychiatric disorders ANXIETY subjects affected / exposed occurrences (all) | 7 / 232 (3.02%) 7 | 32 / 473 (6.77%) 32 | |
| DEPRESSION subjects affected / exposed occurrences (all) | 5 / 232 (2.16%) 5 | 29 / 473 (6.13%) 29 | |
| INSOMNIA subjects affected / exposed occurrences (all) | 31 / 232 (13.36%) 33 | 70 / 473 (14.80%) 76 | |
| Investigations ALANINE AMINOTRANSFERASE INCREASED subjects affected / exposed occurrences (all) | 14 / 232 (6.03%) 18 | 26 / 473 (5.50%) 42 | |
| BLOOD CREATININE INCREASED subjects affected / exposed occurrences (all) | 8 / 232 (3.45%) 13 | 27 / 473 (5.71%) 32 | |
| NEUTROPHIL COUNT DECREASED subjects affected / exposed occurrences (all) | 35 / 232 (15.09%) 62 | 93 / 473 (19.66%) 188 | |
| PLATELET COUNT DECREASED subjects affected / exposed occurrences (all) | 38 / 232 (16.38%) 61 | 108 / 473 (22.83%) 179 | |
| WEIGHT DECREASED subjects affected / exposed occurrences (all) | 28 / 232 (12.07%) 29 | 63 / 473 (13.32%) 71 | |
| WHITE BLOOD CELL COUNT DECREASED subjects affected / exposed occurrences (all) | 18 / 232 (7.76%) 28 | 49 / 473 (10.36%) 80 | |
| Injury, poisoning and procedural complications | | | |

| | | | |
|--|----------------------|------------------------|--|
| FALL subjects affected / exposed occurrences (all) | 4 / 232 (1.72%) 4 | 24 / 473 (5.07%) 33 | |
| Nervous system disorders | | | |
| DIZZINESS | | | |
| subjects affected / exposed | 25 / 232 (10.78%) | 78 / 473 (16.49%) | |
| occurrences (all) | 36 | 90 | |
| DYSGEUSIA | | | |
| subjects affected / exposed | 12 / 232 (5.17%) | 43 / 473 (9.09%) | |
| occurrences (all) | 12 | 46 | |
| HEADACHE | | | |
| subjects affected / exposed | 23 / 232 (9.91%) | 85 / 473 (17.97%) | |
| occurrences (all) | 26 | 106 | |
| NEUROPATHY PERIPHERAL | | | |
| subjects affected / exposed | 22 / 232 (9.48%) | 56 / 473 (11.84%) | |
| occurrences (all) | 26 | 58 | |
| PARAESTHESIA | | | |
| subjects affected / exposed | 12 / 232 (5.17%) | 43 / 473 (9.09%) | |
| occurrences (all) | 13 | 51 | |
| PERIPHERAL SENSORY NEUROPATHY | | | |
| subjects affected / exposed | 23 / 232 (9.91%) | 60 / 473 (12.68%) | |
| occurrences (all) | 29 | 71 | |
| Blood and lymphatic system disorders | | | |
| ANAEMIA | | | |
| subjects affected / exposed | 117 / 232 (50.43%) | 259 / 473 (54.76%) | |
| occurrences (all) | 134 | 357 | |
| LEUKOPENIA | | | |
| subjects affected / exposed | 19 / 232 (8.19%) | 51 / 473 (10.78%) | |
| occurrences (all) | 29 | 92 | |
| NEUTROPENIA | | | |
| subjects affected / exposed | 105 / 232 (45.26%) | 213 / 473 (45.03%) | |
| occurrences (all) | 194 | 424 | |
| THROMBOCYTOPENIA | | | |
| subjects affected / exposed | 60 / 232 (25.86%) | 132 / 473 (27.91%) | |
| occurrences (all) | 96 | 210 | |
| Eye disorders | | | |

| | | | |
|--|---------------------------|---------------------------|--|
| VISION BLURRED subjects affected / exposed occurrences (all) | 6 / 232 (2.59%) 6 | 25 / 473 (5.29%) 28 | |
| Gastrointestinal disorders | | | |
| ABDOMINAL PAIN subjects affected / exposed occurrences (all) | 17 / 232 (7.33%) 20 | 54 / 473 (11.42%) 67 | |
| CONSTIPATION subjects affected / exposed occurrences (all) | 71 / 232 (30.60%) 89 | 176 / 473 (37.21%) 224 | |
| DIARRHOEA subjects affected / exposed occurrences (all) | 72 / 232 (31.03%) 102 | 196 / 473 (41.44%) 321 | |
| DYSPEPSIA subjects affected / exposed occurrences (all) | 7 / 232 (3.02%) 8 | 33 / 473 (6.98%) 34 | |
| NAUSEA subjects affected / exposed occurrences (all) | 105 / 232 (45.26%) 150 | 236 / 473 (49.89%) 354 | |
| STOMATITIS subjects affected / exposed occurrences (all) | 12 / 232 (5.17%) 14 | 40 / 473 (8.46%) 45 | |
| VOMITING subjects affected / exposed occurrences (all) | 43 / 232 (18.53%) 68 | 130 / 473 (27.48%) 228 | |
| ABDOMINAL PAIN UPPER subjects affected / exposed occurrences (all) | 11 / 232 (4.74%) 14 | 25 / 473 (5.29%) 33 | |
| DRY MOUTH subjects affected / exposed occurrences (all) | 5 / 232 (2.16%) 5 | 24 / 473 (5.07%) 24 | |
| GASTROESOPHAGEAL REFLUX DISEASE subjects affected / exposed occurrences (all) | 6 / 232 (2.59%) 7 | 24 / 473 (5.07%) 25 | |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|-------------------|--------------------|--|
| ALOPECIA | | | |
| subjects affected / exposed | 63 / 232 (27.16%) | 152 / 473 (32.14%) | |
| occurrences (all) | 63 | 155 | |
| DRY SKIN | | | |
| subjects affected / exposed | 12 / 232 (5.17%) | 28 / 473 (5.92%) | |
| occurrences (all) | 12 | 31 | |
| PRURITUS | | | |
| subjects affected / exposed | 12 / 232 (5.17%) | 61 / 473 (12.90%) | |
| occurrences (all) | 12 | 81 | |
| RASH | | | |
| subjects affected / exposed | 17 / 232 (7.33%) | 73 / 473 (15.43%) | |
| occurrences (all) | 19 | 86 | |
| Endocrine disorders | | | |
| HYPOTHYROIDISM | | | |
| subjects affected / exposed | 1 / 232 (0.43%) | 51 / 473 (10.78%) | |
| occurrences (all) | 1 | 55 | |
| Musculoskeletal and connective tissue disorders | | | |
| ARTHRALGIA | | | |
| subjects affected / exposed | 36 / 232 (15.52%) | 113 / 473 (23.89%) | |
| occurrences (all) | 40 | 161 | |
| BACK PAIN | | | |
| subjects affected / exposed | 16 / 232 (6.90%) | 89 / 473 (18.82%) | |
| occurrences (all) | 16 | 105 | |
| MUSCULAR WEAKNESS | | | |
| subjects affected / exposed | 14 / 232 (6.03%) | 25 / 473 (5.29%) | |
| occurrences (all) | 16 | 27 | |
| MYALGIA | | | |
| subjects affected / exposed | 10 / 232 (4.31%) | 50 / 473 (10.57%) | |
| occurrences (all) | 12 | 60 | |
| PAIN IN EXTREMITY | | | |
| subjects affected / exposed | 15 / 232 (6.47%) | 61 / 473 (12.90%) | |
| occurrences (all) | 15 | 72 | |
| Infections and infestations | | | |
| BRONCHITIS | | | |
| subjects affected / exposed | 6 / 232 (2.59%) | 29 / 473 (6.13%) | |
| occurrences (all) | 7 | 30 | |

| | | | |
|------------------------------------|-------------------|--------------------|--|
| NASOPHARYNGITIS | | | |
| subjects affected / exposed | 10 / 232 (4.31%) | 38 / 473 (8.03%) | |
| occurrences (all) | 11 | 61 | |
| PNEUMONIA | | | |
| subjects affected / exposed | 8 / 232 (3.45%) | 37 / 473 (7.82%) | |
| occurrences (all) | 8 | 41 | |
| UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 12 / 232 (5.17%) | 35 / 473 (7.40%) | |
| occurrences (all) | 15 | 55 | |
| URINARY TRACT INFECTION | | | |
| subjects affected / exposed | 19 / 232 (8.19%) | 63 / 473 (13.32%) | |
| occurrences (all) | 20 | 91 | |
| Metabolism and nutrition disorders | | | |
| DECREASED APPETITE | | | |
| subjects affected / exposed | 64 / 232 (27.59%) | 144 / 473 (30.44%) | |
| occurrences (all) | 70 | 169 | |
| DEHYDRATION | | | |
| subjects affected / exposed | 25 / 232 (10.78%) | 52 / 473 (10.99%) | |
| occurrences (all) | 35 | 73 | |
| HYPOKALAEMIA | | | |
| subjects affected / exposed | 24 / 232 (10.34%) | 77 / 473 (16.28%) | |
| occurrences (all) | 29 | 98 | |
| HYPOMAGNESAEMIA | | | |
| subjects affected / exposed | 40 / 232 (17.24%) | 94 / 473 (19.87%) | |
| occurrences (all) | 50 | 130 | |
| HYPONATRAEMIA | | | |
| subjects affected / exposed | 8 / 232 (3.45%) | 31 / 473 (6.55%) | |
| occurrences (all) | 10 | 54 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 24 August 2015 | <p>Protocol was amended to include change to the name of the test product from MPDL3280A to atezolizumab. The evaluations of progression-free survival at 6 months and at 1 year and overall survival at 3 years have been added as exploratory objectives to further evaluate the clinical benefit of atezolizumab at these time points. The contraception requirements in the inclusion and exclusion criteria and the pregnancy-reporting information have been updated to be consistent with safety information for nab-paclitaxel. The study inclusion criteria have been modified, on the basis of data from an expanding safety database, to allow for patients with treated, asymptomatic cerebellar metastases to be enrolled provided specific criteria are met. The exclusion criteria for history of autoimmune disease has been broadened, on the basis of data from an expanding safety database, to allow for patients with eczema, psoriasis, or lichen simplex chronicus or vitiligo with dermatologic manifestations only to be permitted provided that they meet the specific conditions. The study exclusion criterion regarding treatment with systemic immunostimulatory agents within 6 weeks or 5 half-lives of the drug (whichever is shorter) prior to randomization has been modified to 4 weeks prior to randomization for consistency with more recent atezolizumab protocols. The exclusion criterion specifying that patients with a history of allergic reaction to intravenous contrast that requires steroid pretreatment should have baseline and subsequent tumor assessments performed via magnetic resonance imaging (MRI) has been removed because this is in conflict with Section 4.5.5. Patients with contraindications to contrast may have assessments done with non-contrast computed tomography or MRI.</p> |
| 11 November 2015 | <p>Protocol was amended to clarify that a wash-out period of at least 4 weeks or five half-lives, whichever is longer, of any systemic immunomodulatory agent is required prior to enrollment.</p> |
| 15 June 2016 | <p>Protocol was amended to add a co-primary endpoint of overall survival (OS) to the progression-free survival (PFS) primary endpoint. For patients consented and randomized to Arm B after Ethics Committee or Institutional Review Board approval of Protocol GO29537, Version 5 at each respective site, the option for crossover to atezolizumab maintenance therapy has been removed to enable the comparative analyses of the two treatment arms. Patients randomized to Arm B who were consented under previous versions of this protocol prior to the approval of Version 5 will continue to have the option for crossover to atezolizumab maintenance therapy. The total number of patients to be randomized in the study has increased from 550 patients to 650 patients to ensure that the study is adequately powered for the comparative analyses. Erlotinib switch maintenance therapy has been removed from the protocol. A secondary efficacy objective and outcome measure has been added to evaluate the efficacy of atezolizumab + carboplatin + nab-paclitaxel compared with carboplatin + nab-paclitaxel as measured by investigator-assessed time to response (TTR) according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) for both the intent-to-treat (ITT) and programmed death–ligand 1(PD-L1)–selected populations.</p> |

| | |
|-----------------|---|
| 01 March 2017 | Protocol was amended to include change to the primary analysis populations for the co-primary endpoints of progression-free survival (PFS) and overall survival (OS). OS will be analyzed in the intent-to-treat (ITT) population. PFS will be analyzed in the ITT population and a population with a defined level of expression of a PD-L1 and T-effector gene signature in tumor tissue as determined by an RNA-based assay. Patients with known sensitizing EGFR mutations or ALK translocations will be excluded from the primary analysis populations. The analyses of PFS and OS in all randomized patients will be conducted as secondary analyses. Additional censoring rule for the primary endpoint of PFS for U.S. registration purposes has been removed. The statistical testing procedures have been amended to reflect the change in analysis populations. All endpoints (secondary and exploratory) based on the review by an Independent Review Facility (IRF) have been removed. |
| 24 October 2018 | Protocol was amended to correct the end of study definition corrected. This correction ensures that the study continues until last patient, last visit or until the Sponsor terminates the study. The inclusion criterion that addresses female contraception has been modified to specify when women must refrain from donating eggs. |
| 29 March 2019 | Protocol was amended to clarify the inclusion criterion on contraception. In addition, reporting for serious adverse events and adverse events of special interest has been extended to 90 days after last dose of study treatment or until initiation of a new anticancer therapy, whichever occurs first. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported