



Clinical trial results:

A randomized, double-blinded, phase III study of atezolizumab versus placebo in patients with late relapse of epithelial ovarian, fallopian tube, or peritoneal cancer treated by platinum-based chemotherapy and bevacizumab

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2015-005471-24 |
| Trial protocol | FR ES AT DE BE CZ |
| Global end of trial date | 22 February 2024 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 10 April 2025 |
| First version publication date | 10 April 2025 |

Trial information

Trial identification

| | |
|-----------------------|---------------|
| Sponsor protocol code | GINECO-OV236b |
|-----------------------|---------------|

Additional study identifiers

| | |
|------------------------------------|-------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02891824 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | ENGOT-ov29: ENGOT |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | ARCAGY-GINECO |
| Sponsor organisation address | 8 rue Lamennais, Paris, France, 75008 |
| Public contact | Marina Gomes, projet manager, ARCAGY-GINECO, +33 184852020, contact@arcagy.org |
| Scientific contact | Marina Gomes, projet manager, ARCAGY-GINECO, +33 184852020, contact@arcagy.org |

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 | 22 February 2024 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 22 February 2024 |
| Global end of trial reached? | Yes |
| Global end of trial date | 22 February 2024 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy of combining atezolizumab with carboplatin-based chemotherapy and bevacizumab compared to placebo with carboplatin-based chemotherapy and bevacizumab in patients with late (platinum-sensitive) relapse of epithelial ovarian, fallopian tube, or peritoneal cancer. Co-Primary outcomes will be the Progression Free Survival (PFS1) in the ITT population and in the PD-L1 positive subpopulation (PD-L1 expression $\geq 1\%$).

The primary endpoint measure is progression free survival (PFS1), where the date of progression is based on investigator assessment using the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1).

Protection of trial subjects:

The study was performed in accordance with ethical principles that have their origin in the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and are consistent with International Conference on Harmonization (ICH)/Good Clinical Practice (GCP) and applicable regulatory requirements. Informed consent was obtained before inclusion in the study.

All patients were treated with the standard of care for patients with a relapse from ovarian cancer and placebo or atezolizumab was added. Disease progression was a criterion for study end, so patients not correctly treated by the study treatment exited the study and were treated with other options.

Background therapy:

Platinum-based chemotherapy either :

- Carboplatin (AUC = 4, d1) combined with gemcitabine (1000 mg/m², d1 & d8) and bevacizumab (15mg/kg, d1) + placebo (1200mg, d1) x 6 cycles q3wk followed by maintenance with bevacizumab (15 mg/kg, d1) + placebo (1200mg, d1) q3w or
- Carboplatin (AUC = 5, d1) combined with paclitaxel (175 mg/m², d1) and bevacizumab (15mg/kg, d1) + placebo (1200mg, d1) x 6 cycles every 3wk followed by maintenance with bevacizumab (15 mg/kg, d1) + placebo (1200mg, d1) q3w or
- Carboplatin (AUC = 5, d1) combined with pegylated liposomal doxorubicin (PLD) (30 mg/m², d1) and bevacizumab (10mg/kg, d1 & 15) + placebo (800mg, d1& 15) x 6 cycles every 4wk followed by maintenance with bevacizumab (15 mg/kg, d1) + placebo (1200mg, d1) q3w.

Evidence for comparator:

Atezolizumab was compared to a placebo. In both groups patients were also treated with bevacizumab and a platinum-based chemotherapy.

| | |
|---|-------------------|
| Actual start date of recruitment | 28 September 2016 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Spain: 67 |
| Country: Number of subjects enrolled | Austria: 24 |

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Belgium: 3 |
| Country: Number of subjects enrolled | Czechia: 8 |
| Country: Number of subjects enrolled | France: 441 |
| Country: Number of subjects enrolled | Germany: 70 |
| Country: Number of subjects enrolled | Israel: 1 |
| Worldwide total number of subjects | 614 |
| EEA total number of subjects | 613 |

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) | 342 |
| From 65 to 84 years | 272 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

787 patients were included from 25/09/2016 to 04/10/2019 and 614 patients were randomized from 07/10/2016 to 15/10/2019.

Pre-assignment

Screening details:

787 patients were screened and 173 were excluded before randomization (n=93 for not meeting the inclusion criteria, n=27 for tumor block unavailability, n=7 for adverse events, n= 21 withdrew their consent, n= 2 were lost to follow-up and n= 23 for other reasons).

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Blinding implementation details:

Atezolizumab and placebo treatment were double blinded. The study medication was labelled using a unique kit ID number, which was linked to the randomization scheme. The active and placebo kits were presented in the same packaging to ensure blinding of the study medication.

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo |

Arm description:

Placebo + bevacizumab & platinum-based chemotherapy

The placebo arm included one of 3 following regimens up to investigator choice (chosen prior to randomization)

d) Carboplatin (AUC = 4, d1) combined with gemcitabine (1000 mg/m², d1 & d8) and bevacizumab (15mg/kg, d1) + placebo (1200mg, d1) x 6 cycles q3wk followed by maintenance with bevacizumab (15 mg/kg, d1) + placebo (1200mg, d1) q3w or

e) Carboplatin (AUC = 5, d1) combined with paclitaxel (175 mg/m², d1) and bevacizumab (15mg/kg, d1) + placebo (1200mg, d1) x 6 cycles every 3wk followed by maintenance with bevacizumab (15 mg/kg, d1) + placebo (1200mg, d1) q3w or

f) Carboplatin (AUC = 5, d1) combined with pegylated liposomal doxorubicin (PLD) (30 mg/m², d1) and bevacizumab (10mg/kg, d1 & 15) + placebo (800mg, d1& 15) x 6 cycles every 4wk followed by maintenance with bevacizumab (15 mg/kg, d1) + placebo (1200mg, d1) q3w.

| | |
|--|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

The fixed dose of 1200 mg (equivalent to an average body weight-based dose of 15 mg/kg) was selected based on both nonclinical studies and available clinical data. This atezolizumab/placebo 1200mg dose was delivered every 3 weeks before bevacizumab infusion and prior to the carboplatin-gemcitabine or paclitaxel regimen and in all the maintenance schedule. The atezolizumab/placebo dose was 800mg every 2 weeks when delivered with carboplatin-PLD chemotherapy.

| | |
|-----------|--------------|
| Arm title | Atezolizumab |
|-----------|--------------|

Arm description:

Atezolizumab + bevacizumab & platinum-based chemotherapy

The atezolizumab arm included one of 3 following regimens up to investigator choice (chosen prior to randomization)

- a) Carboplatin (AUC = 4, d1) combined with gemcitabine (1000 mg/m², d1 & d8) and bevacizumab (15mg/kg, d1) + atezolizumab (1200mg, d1) x 6 cycles q3wk followed by maintenance with bevacizumab (15 mg/kg, d1) + atezolizumab (1200mg, d1) q3w or
- b) Carboplatin (AUC = 5, d1) combined with paclitaxel (175 mg/m², d1) and bevacizumab (15mg/kg, d1) + atezolizumab (1200mg, d1) x 6 cycles every 3wk followed by maintenance with bevacizumab (15 mg/kg, d1) + atezolizumab (1200mg, d1) q3w or
- c) Carboplatin (AUC = 5, d1) combined with pegylated liposomal doxorubicin (PLD) (30 mg/m², d1) and bevacizumab (10mg/kg, d1 & 15) + atezolizumab (800mg, d1& 15) x 6 cycles every 4wk followed by maintenance with bevacizumab (15 mg/kg, d1) + atezolizumab (1200mg, d1) q3w.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Atezolizumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

The fixed dose of 1200 mg (equivalent to an average body weight–based dose of 15 mg/kg) was selected based on both nonclinical studies and available clinical data. This atezolizumab/placebo 1200mg dose was delivered every 3 weeks before bevacizumab infusion and prior to the carboplatin-gemcitabine or paclitaxel regimen and in all the maintenance schedule. The atezolizumab/placebo dose was 800mg every 2 weeks when delivered with carboplatin-PLD chemotherapy.

| Number of subjects in period 1 | Placebo | Atezolizumab |
|---------------------------------------|---------|--------------|
| Started | 204 | 410 |
| Completed | 204 | 410 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo + bevacizumab & platinum-based chemotherapy

The placebo arm included one of 3 following regimens up to investigator choice (chosen prior to randomization)

d) Carboplatin (AUC = 4, d1) combined with gemcitabine (1000 mg/m², d1 & d8) and bevacizumab (15mg/kg, d1) + placebo (1200mg, d1) x 6 cycles q3wk followed by maintenance with bevacizumab (15 mg/kg, d1) + placebo (1200mg, d1) q3w or

e) Carboplatin (AUC = 5, d1) combined with paclitaxel (175 mg/m², d1) and bevacizumab (15mg/kg, d1) + placebo (1200mg, d1) x 6 cycles every 3wk followed by maintenance with bevacizumab (15 mg/kg, d1) + placebo (1200mg, d1) q3w or

f) Carboplatin (AUC = 5, d1) combined with pegylated liposomal doxorubicin (PLD) (30 mg/m², d1) and bevacizumab (10mg/kg, d1 & 15) + placebo (800mg, d1& 15) x 6 cycles every 4wk followed by maintenance with bevacizumab (15 mg/kg, d1) + placebo (1200mg, d1) q3w.

| | |
|-----------------------|--------------|
| Reporting group title | Atezolizumab |
|-----------------------|--------------|

Reporting group description:

Atezolizumab + bevacizumab & platinum-based chemotherapy

The atezolizumab arm included one of 3 following regimens up to investigator choice (chosen prior to randomization)

a) Carboplatin (AUC = 4, d1) combined with gemcitabine (1000 mg/m², d1 & d8) and bevacizumab (15mg/kg, d1) + atezolizumab (1200mg, d1) x 6 cycles q3wk followed by maintenance with bevacizumab (15 mg/kg, d1) + atezolizumab (1200mg, d1) q3w or

b) Carboplatin (AUC = 5, d1) combined with paclitaxel (175 mg/m², d1) and bevacizumab (15mg/kg, d1) + atezolizumab (1200mg, d1) x 6 cycles every 3wk followed by maintenance with bevacizumab (15 mg/kg, d1) + atezolizumab (1200mg, d1) q3w or

c) Carboplatin (AUC = 5, d1) combined with pegylated liposomal doxorubicin (PLD) (30 mg/m², d1) and bevacizumab (10mg/kg, d1 & 15) + atezolizumab (800mg, d1& 15) x 6 cycles every 4wk followed by maintenance with bevacizumab (15 mg/kg, d1) + atezolizumab (1200mg, d1) q3w.

| Reporting group values | Placebo | Atezolizumab | Total |
|---|---------|--------------|-------|
| Number of subjects | 204 | 410 | 614 |
| Age categorical Units: Subjects | | | |
| In utero | | | 0 |
| Preterm newborn infants (gestational age < 37 wks) | | | 0 |
| Newborns (0-27 days) | | | 0 |
| Infants and toddlers (28 days-23 months) | | | 0 |
| Children (2-11 years) | | | 0 |
| Adolescents (12-17 years) | | | 0 |
| Adults (18-64 years) | | | 0 |
| From 65-84 years | | | 0 |
| 85 years and over | | | 0 |
| Age continuous Units: years | | | |
| median | 62.54 | 61.76 | |
| standard deviation | ± 10.82 | ± 10.75 | - |
| Gender categorical Units: Subjects | | | |
| Female | 204 | 410 | 614 |
| Male | 0 | 0 | 0 |

| | | | |
|---|-----|-----|-----|
| ECOG | | | |
| Units: Subjects | | | |
| score of 0 | 131 | 277 | 408 |
| score of 1 | 72 | 131 | 203 |
| score of 2 | 0 | 2 | 2 |
| score of 3 | 0 | 0 | 0 |
| score of 4 | 0 | 0 | 0 |
| NA | 1 | 0 | 1 |
| CA125 dosage before treatment administration | | | |
| Units: Subjects | | | |
| Anormal <100 kU/L | 48 | 88 | 136 |
| Anormal ≥100 kU/L | 113 | 227 | 340 |
| Normal | 43 | 92 | 135 |
| NA | 0 | 3 | 3 |
| Blood Pressure | | | |
| Units: Subjects | | | |
| High (SBP > 140 and DPB >90) | 9 | 12 | 21 |
| Normal | 193 | 395 | 588 |
| NA | 2 | 3 | 5 |
| PDL1 expression | | | |
| PD-L1-positive status was defined as tumor-infiltrating immune cell (IC) PD-L1 expression on ≥1% of tumor area using the Ventana SP142 immunohistochemistry assay (Ventana Medical Systems, Tucson, AZ), as in previous atezolizumab trials (Moore et al. 2021; Schmid et al. 2018; Mittendorf et al. 2020; Miles et al. 2021). | | | |
| Units: Subjects | | | |
| Positive | 77 | 156 | 233 |
| Negative | 102 | 196 | 298 |
| Inconclusive | 25 | 58 | 83 |
| Primary cancer site | | | |
| Units: Subjects | | | |
| Ovary | 191 | 369 | 560 |
| Fallopian tube | 5 | 27 | 32 |
| Peritoneal | 8 | 14 | 22 |
| Adenocarcinoma type | | | |
| Units: Subjects | | | |
| Serous High Grade (a) | 169 | 346 | 515 |
| Serous Low Grade (b) | 8 | 32 | 40 |
| Endometrioid Grade 2/3 (c) | 11 | 12 | 23 |
| Endometrioid Grade 1 (d) | 0 | 1 | 1 |
| Clear cell | 9 | 8 | 17 |
| Mucinous | 0 | 0 | 0 |
| Undifferentiated | 4 | 4 | 8 |
| Other | 1 | 1 | 2 |
| Carcinosarcoma | 1 | 4 | 5 |
| Mixed tumor | 0 | 2 | 2 |
| Brenner | 1 | 0 | 1 |
| FIGO | | | |
| Units: Subjects | | | |
| Stage I | 5 | 18 | 23 |
| Stage II | 8 | 18 | 26 |
| Stage III | 117 | 261 | 378 |

| | | | |
|--|----------------|----------------|-----|
| Stage IV | 49 | 73 | 122 |
| Unknown | 25 | 40 | 65 |
| BRCA mutation status | | | |
| Units: Subjects | | | |
| Germline or somatic mutation | 32 | 40 | 72 |
| Inconclusive | 54 | 129 | 183 |
| No mutation | 118 | 241 | 359 |
| Debulking surgery | | | |
| Units: Subjects | | | |
| No | 21 | 27 | 48 |
| Yes | 183 | 383 | 566 |
| Number of previous lines of treatment | | | |
| Units: Subjects | | | |
| 1 line | 147 | 307 | 454 |
| 2 lines | 56 | 103 | 159 |
| 3 lines | 1 | 0 | 1 |
| Tumor size | | | |
| Units: millimetre(s) | | | |
| median | 38.5 | 47 | |
| inter-quartile range (Q1-Q3) | 24 to 68 | 28 to 82.75 | - |
| BMI | | | |
| kg/cm2 | | | |
| Units: kilogram(s)/square centimetre | | | |
| median | 24.27 | 24.67 | |
| inter-quartile range (Q1-Q3) | 21.62 to 27.99 | 21.61 to 28.23 | - |
| Time between relapse before entering the study and randomization | | | |
| Units: day | | | |
| median | 57 | 59 | |
| inter-quartile range (Q1-Q3) | 41 to 78 | 42 to 82 | - |

End points

End points reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo + bevacizumab & platinum-based chemotherapy

The placebo arm included one of 3 following regimens up to investigator choice (chosen prior to randomization)

d) Carboplatin (AUC = 4, d1) combined with gemcitabine (1000 mg/m², d1 & d8) and bevacizumab (15mg/kg, d1) + placebo (1200mg, d1) x 6 cycles q3wk followed by maintenance with bevacizumab (15 mg/kg, d1) + placebo (1200mg, d1) q3w or

e) Carboplatin (AUC = 5, d1) combined with paclitaxel (175 mg/m², d1) and bevacizumab (15mg/kg, d1) + placebo (1200mg, d1) x 6 cycles every 3wk followed by maintenance with bevacizumab (15 mg/kg, d1) + placebo (1200mg, d1) q3w or

f) Carboplatin (AUC = 5, d1) combined with pegylated liposomal doxorubicin (PLD) (30 mg/m², d1) and bevacizumab (10mg/kg, d1 & 15) + placebo (800mg, d1& 15) x 6 cycles every 4wk followed by maintenance with bevacizumab (15 mg/kg, d1) + placebo (1200mg, d1) q3w.

| | |
|-----------------------|--------------|
| Reporting group title | Atezolizumab |
|-----------------------|--------------|

Reporting group description:

Atezolizumab + bevacizumab & platinum-based chemotherapy

The atezolizumab arm included one of 3 following regimens up to investigator choice (chosen prior to randomization)

a) Carboplatin (AUC = 4, d1) combined with gemcitabine (1000 mg/m², d1 & d8) and bevacizumab (15mg/kg, d1) + atezolizumab (1200mg, d1) x 6 cycles q3wk followed by maintenance with bevacizumab (15 mg/kg, d1) + atezolizumab (1200mg, d1) q3w or

b) Carboplatin (AUC = 5, d1) combined with paclitaxel (175 mg/m², d1) and bevacizumab (15mg/kg, d1) + atezolizumab (1200mg, d1) x 6 cycles every 3wk followed by maintenance with bevacizumab (15 mg/kg, d1) + atezolizumab (1200mg, d1) q3w or

c) Carboplatin (AUC = 5, d1) combined with pegylated liposomal doxorubicin (PLD) (30 mg/m², d1) and bevacizumab (10mg/kg, d1 & 15) + atezolizumab (800mg, d1& 15) x 6 cycles every 4wk followed by maintenance with bevacizumab (15 mg/kg, d1) + atezolizumab (1200mg, d1) q3w.

| | |
|----------------------------|------------------------|
| Subject analysis set title | PD-L1 positive Placebo |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

PD-L1 expression was assessed by immunochemistry on immune cells of the tumor de novo biopsy obtained before entry in ATALANTE. PD-L1 positivity was defined as $\geq 1\%$ of immune cells (ICs) expressing PD-L1 which was referred to IC1/2/3 according to PD-L1 scoring algorithm.

| | |
|----------------------------|----------------------------|
| Subject analysis set title | PD-L1 positive Atzolizumab |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

PD-L1 expression was assessed by immunochemistry on immune cells of the tumor de novo biopsy obtained before entry in ATALANTE. PD-L1 positivity was defined as $\geq 1\%$ of immune cells (ICs) expressing PD-L1 which was referred to IC1/2/3 according to PD-L1 scoring algorithm.

Primary: Progression free survival

| | |
|-----------------|---------------------------|
| End point title | Progression free survival |
|-----------------|---------------------------|

End point description:

The co-primary endpoints were not reached and therefore the statistics for the secondary endpoints are not detailed here.

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

End point timeframe:

Progression free survival was assessed over the entire duration of the study from 25/09/2016 to 15/10/2023.

| End point values | Placebo | Atezolizumab | PD-L1 positive Placebo | PD-L1 positive Atzolizumab |
|----------------------------------|------------------------|------------------------|------------------------|----------------------------|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 204 | 410 | 77 | 156 |
| Units: month | | | | |
| median (confidence interval 95%) | 11.27 (11.04 to 13.50) | 13.60 (12.32 to 14.29) | 13.08 (11.40 to 16.49) | 15.24 (13.14 to 17.02) |

Statistical analyses

| | |
|---|-------------------------------------|
| Statistical analysis title | Cox model results in ITT population |
| Comparison groups | Placebo v Atezolizumab |
| Number of subjects included in analysis | 614 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.035 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.83 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.69 |
| upper limit | 0.98 |

| | |
|---|---|
| Statistical analysis title | Cox model in PD-L1 positive population |
| Comparison groups | PD-L1 positive Placebo v PD-L1 positive Atzolizumab |
| Number of subjects included in analysis | 233 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4 |
| Method | Cox model |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.88 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.65 |
| upper limit | 1.18 |

Secondary: Treatment exposure

| | |
|------------------------|--------------------|
| End point title | Treatment exposure |
| End point description: | |
| End point type | Secondary |

End point timeframe:

From start of trial until date of data cut-off (10/15/2023)

| End point values | Placebo | Atezolizumab | | |
|---------------------------------------|----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 202 | 407 | | |
| Units: month | | | | |
| median (inter-quartile range (Q1-Q3)) | 11.2 (8.41 to 16.74) | 11.33 (7.06 to 18.28) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

| | |
|---------------------------------------|------------------|
| End point title | Overall survival |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Over the whole duration of the study. | |

| End point values | Placebo | Atezolizumab | PD-L1 positive Placebo | PD-L1 positive Atezolizumab |
|----------------------------------|------------------------|------------------------|------------------------|-----------------------------|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 204 | 410 | 77 | 156 |
| Units: percent | | | | |
| number (confidence interval 95%) | 30.62 (27.79 to 33.15) | 35.75 (32.89 to 41.00) | 33.68 (30.62 to 50.76) | 42.97 (38.05 to 50.23) |

Statistical analyses

| | |
|---|-------------------------------------|
| Statistical analysis title | Cox model results in ITT population |
| Statistical analysis description: | |
| The proportional hazard assumption was tested using Likelihood ratio test on time-dependent coefficient. The test statistic for the likelihood ratio test between the time independent and time dependent models was 1.422. With one degree of freedom, the corresponding p value is equal to 0.233, therefore the time dependent coefficient is non-significant. Based on this result, an adjusted Cox model without time varying effect of treatment was used for the analysis on the ITT population. | |
| Comparison groups | Placebo v Atezolizumab |

| | |
|---|-------------------|
| Number of subjects included in analysis | 614 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.83 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.69 |
| upper limit | 0.98 |

| | |
|---|---|
| Statistical analysis title | Cox model results in PD-L1 positive population |
| Comparison groups | PD-L1 positive Placebo v PD-L1 positive Atzolizumab |
| Number of subjects included in analysis | 233 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.84 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.6 |
| upper limit | 1.17 |

Secondary: Time to first subsequent therapy

| | |
|--------------------------------------|----------------------------------|
| End point title | Time to first subsequent therapy |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Over the whole duration of the trial | |

| End point values | Placebo | Atezolizumab | PD-L1 positive Placebo | PD-L1 positive Atzolizumab |
|----------------------------------|------------------------|------------------------|------------------------|----------------------------|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 204 | 410 | 77 | 156 |
| Units: month | | | | |
| median (confidence interval 95%) | 12.42 (11.83 to 14.42) | 14.36 (13.67 to 15.64) | 14.16 (12.02 to 18.43) | 17.12 (14.36 to 19.98) |

Statistical analyses

| | |
|---|-------------------------------------|
| Statistical analysis title | Cox model results in ITT population |
| Comparison groups | Placebo v Atezolizumab |
| Number of subjects included in analysis | 614 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.83 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.69 |
| upper limit | 0.99 |

| | |
|---|---|
| Statistical analysis title | Cox model in PD-L1 positive population |
| Comparison groups | PD-L1 positive Placebo v PD-L1 positive Atzolizumab |
| Number of subjects included in analysis | 233 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.89 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.66 |
| upper limit | 1.19 |

Secondary: Time to second subsequent therapy

| | |
|--|-----------------------------------|
| End point title | Time to second subsequent therapy |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Endpoint was assessed over the entire duration of the study from 25/09/2016 to 15/10/2023. | |

| End point values | Placebo | Atezolizumab | PD-L1 positive Placebo | PD-L1 positive Atzolizumab |
|----------------------------------|------------------------|------------------------|------------------------|----------------------------|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 204 | 410 | 77 | 156 |
| Units: month | | | | |
| median (confidence interval 95%) | 20.99 (18.63 to 23.75) | 23.72 (22.60 to 25.72) | 25.26 (21.62 to 31.18) | 27.14 (24.61 to 33.08) |

Statistical analyses

| | |
|---|-------------------------------------|
| Statistical analysis title | Cox model results in ITT population |
| Comparison groups | Placebo v Atezolizumab |
| Number of subjects included in analysis | 614 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.83 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.69 |
| upper limit | 0.99 |

| | |
|---|--|
| Statistical analysis title | Cox model in PD-L1 positive population |
| Comparison groups | PD-L1 positive Placebo v PD-L1 positive Atezolizumab |
| Number of subjects included in analysis | 233 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.97 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.71 |
| upper limit | 1.32 |

Secondary: Time to RECIST progression or CA125 deterioration

| | |
|---|---|
| End point title | Time to RECIST progression or CA125 deterioration |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Was assessed over the entire duration of the study from 25/09/2016 to 15/10/2023. | |

| End point values | Placebo | Atezolizumab | PD-L1 positive Placebo | PD-L1 positive Atzolizumab |
|----------------------------------|------------------------|------------------------|------------------------|----------------------------|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 204 | 410 | 77 | 156 |
| Units: month | | | | |
| median (confidence interval 95%) | 10.81 (10.38 to 11.17) | 11.56 (11.07 to 12.88) | 11.17 (10.64 to 12.45) | 13.70 (12.62 to 16.39) |

Statistical analyses

| | |
|---|-------------------------------------|
| Statistical analysis title | Cox model results in ITT population |
| Comparison groups | Placebo v Atezolizumab |
| Number of subjects included in analysis | 614 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.67 |
| upper limit | 0.95 |

| | |
|---|---|
| Statistical analysis title | Cox model in PD-L1 positive population |
| Comparison groups | PD-L1 positive Placebo v PD-L1 positive Atzolizumab |
| Number of subjects included in analysis | 233 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.73 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.55 |
| upper limit | 0.98 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events will be collected from time of signature of informed consent, throughout the treatment period and up to and including the 30-day follow-up period.

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

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|----|
| Dictionary version | 26 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|-------------------|
| Reporting group title | Safety population |
|-----------------------|-------------------|

Reporting group description:

The safety was described on the safety set population (N=609), including only patients who had at least one dose of study treatment. 5 patients (3 in the atezolizumab group and 2 in the placebo group) did not start bevacizumab nor atezolizumab after randomization.

| Serious adverse events | Safety population | | |
|---|--------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 444 / 609 (72.91%) | | |
| number of deaths (all causes) | 443 | | |
| number of deaths resulting from adverse events | 19 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Acute megakaryocytic leukaemia | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Acute myeloid leukaemia | | | |
| subjects affected / exposed | 3 / 609 (0.49%) | | |
| occurrences causally related to treatment / all | 2 / 3 | | |
| deaths causally related to treatment / all | 2 / 3 | | |
| Adrenal metastases | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Breast cancer | | | |

| | | | |
|---|--------------------|--|--|
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cancer pain | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lymphangitis carcinomatosis | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myelodysplastic syndrome | | | |
| subjects affected / exposed | 4 / 609 (0.66%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Paraneoplastic syndrome | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Aortic stenosis | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypertension | | | |
| subjects affected / exposed | 190 / 609 (31.20%) | | |
| occurrences causally related to treatment / all | 173 / 190 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hematoma | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombosis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 2 / 609 (0.33%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 2 / 609 (0.33%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Embolism | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haematoma | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Malignant hypertension | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Phlebitis | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Venous thrombosis | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |
| Intervertebral disc operation | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary catheter insertion | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Asthenia | | | |
| subjects affected / exposed | 2 / 609 (0.33%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Catheter infection | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Death | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Drug intolerance | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General physical health deterioration | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 10 / 609 (1.64%) | | |
| occurrences causally related to treatment / all | 4 / 10 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Inflammation | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Influenza like illness | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mucositis | | | |
| subjects affected / exposed | 3 / 609 (0.49%) | | |
| occurrences causally related to treatment / all | 2 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Multi organ failure | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Pain | | | |
| subjects affected / exposed | 2 / 609 (0.33%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyrexia | | | |
| subjects affected / exposed | 8 / 609 (1.31%) | | |
| occurrences causally related to treatment / all | 1 / 8 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 7 / 609 (1.15%) | | |
| occurrences causally related to treatment / all | 0 / 7 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anaphylactic reaction | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 2 / 609 (0.33%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anaphylactic shock | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 7 / 609 (1.15%) | | |
| occurrences causally related to treatment / all | 5 / 7 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Rectovaginal fistula | | | |
| subjects affected / exposed | 2 / 609 (0.33%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dyspnea | | | |
| subjects affected / exposed | 5 / 609 (0.82%) | | |
| occurrences causally related to treatment / all | 1 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Embolism pulmonary | | | |
| subjects affected / exposed | 19 / 609 (3.12%) | | |
| occurrences causally related to treatment / all | 12 / 19 | | |
| deaths causally related to treatment / all | 1 / 2 | | |
| Laryngeal spasm | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonitis | | | |
| subjects affected / exposed | 4 / 609 (0.66%) | | |
| occurrences causally related to treatment / all | 4 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lung disorder | | | |
| subjects affected / exposed | 2 / 609 (0.33%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary infarction | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 4 / 609 (0.66%) | | |
| occurrences causally related to treatment / all | 3 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Alkaline phosphatase increased | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 7 / 609 (1.15%) | | |
| occurrences causally related to treatment / all | 6 / 7 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|------------------|--|--|
| CSF white blood cell count decreased | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| GGT increased | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Left ventricular ejection fraction decreased | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Platelet count decreased | | | |
| subjects affected / exposed | 10 / 609 (1.64%) | | |
| occurrences causally related to treatment / all | 2 / 10 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal biopsy | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transaminases increased | | | |
| subjects affected / exposed | 3 / 609 (0.49%) | | |
| occurrences causally related to treatment / all | 3 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| White blood cell decreased | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Cat bite | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|-----------------|--|--|--|
| Eye burns | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Fracture vertebral | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hip fracture | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infusion related reaction | | | | |
| subjects affected / exposed | 3 / 609 (0.49%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intraoperative hemorrhage | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Post biopsy bleeding | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Procedural pneumothorax | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Tendon achilles rupture | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Congenital, familial and genetic disorders | | | | |

| | | | |
|---|-----------------|--|--|
| Aplasia | | | |
| subjects affected / exposed | 2 / 609 (0.33%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 5 / 609 (0.82%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute heart failure | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Cardiac disorder | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac dysfunction | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Cardiac failure | | | |
| subjects affected / exposed | 4 / 609 (0.66%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocardial infarction | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 4 / 609 (0.66%) | | |
| occurrences causally related to treatment / all | 3 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocarditis | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Non ST segment elevation myocardial infarction | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pericardial effusion | | | |
| subjects affected / exposed | 2 / 609 (0.33%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Palpitations | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Cephalgia | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 2 / 609 (0.33%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebral venous thrombosis | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dizziness | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Encephalopathy | | | |
| subjects affected / exposed | 2 / 609 (0.33%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Epileptic seizure | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Headache aggravated | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hemorrhagic stroke | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Hypercapnic coma | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 3 / 609 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ischemic stroke | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Meningismus | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Meningorrhagia | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neurologic disorder NOS | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Posterior reversible encephalopathy syndrome | | | |
| subjects affected / exposed | 2 / 609 (0.33%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Stroke | | | |
| subjects affected / exposed | 3 / 609 (0.49%) | | |
| occurrences causally related to treatment / all | 2 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transient ischemic attack | | | |
| subjects affected / exposed | 3 / 609 (0.49%) | | |
| occurrences causally related to treatment / all | 3 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tremor | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Loss of consciousness | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 10 / 609 (1.64%) | | |
| occurrences causally related to treatment / all | 2 / 10 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aplasia bone marrow | | | |
| subjects affected / exposed | 2 / 609 (0.33%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Febrile aplasia | | | |
| subjects affected / exposed | 8 / 609 (1.31%) | | |
| occurrences causally related to treatment / all | 2 / 8 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Evans syndrome | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 30 / 609 (4.93%) | | |
| occurrences causally related to treatment / all | 6 / 30 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hemolytic anemia | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperviscosity syndrome | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune thrombocytopenic purpura | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutropenia | | | |

| | | | |
|---|-------------------|--|--|
| subjects affected / exposed | 42 / 609 (6.90%) | | |
| occurrences causally related to treatment / all | 10 / 42 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancytopenia | | | |
| subjects affected / exposed | 17 / 609 (2.79%) | | |
| occurrences causally related to treatment / all | 8 / 17 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 68 / 609 (11.17%) | | |
| occurrences causally related to treatment / all | 12 / 68 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombotic microangiopathy | | | |
| subjects affected / exposed | 9 / 609 (1.48%) | | |
| occurrences causally related to treatment / all | 9 / 9 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombotic thrombocytopenic purpura | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Splenic haematoma | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bone marrow failure | | | |
| subjects affected / exposed | 2 / 609 (0.33%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eosinophilia | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ear and labyrinth disorders | | | |
| Labyrinthine hydrops | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 2 / 609 (0.33%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Blurred vision | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Posterior vitreous detachment | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Retinal bleeding | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Uveitis | | | |
| subjects affected / exposed | 3 / 609 (0.49%) | | |
| occurrences causally related to treatment / all | 3 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vitreous hemorrhage | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal hernia | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 8 / 609 (1.31%) | | |
| occurrences causally related to treatment / all | 1 / 8 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute abdomen | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Autoimmune colitis | | | | |
| subjects affected / exposed | 4 / 609 (0.66%) | | | |
| occurrences causally related to treatment / all | 4 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Autoimmune pancreatitis | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bloody stool | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bowel perforation | | | | |
| subjects affected / exposed | 3 / 609 (0.49%) | | | |
| occurrences causally related to treatment / all | 3 / 3 | | | |
| deaths causally related to treatment / all | 1 / 1 | | | |
| Colitis | | | | |
| subjects affected / exposed | 7 / 609 (1.15%) | | | |
| occurrences causally related to treatment / all | 7 / 7 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Colonic fistula | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Constipation | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal motility disorder | | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 22 / 609 (3.61%) | | |
| occurrences causally related to treatment / all | 15 / 22 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Duodenal ulcer | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Enterocutaneous fistula | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Epigastric pain | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal fistula | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Glossitis | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haematemesis | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hemorrhoids | | | |

| | | | | |
|---|------------------|--|--|--|
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hernial eventration | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ileus | | | | |
| subjects affected / exposed | 4 / 609 (0.66%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intestinal obstruction | | | | |
| subjects affected / exposed | 11 / 609 (1.81%) | | | |
| occurrences causally related to treatment / all | 1 / 11 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intestinal perforation | | | | |
| subjects affected / exposed | 4 / 609 (0.66%) | | | |
| occurrences causally related to treatment / all | 1 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intestinal subobstruction | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Mechanical ileus | | | | |
| subjects affected / exposed | 3 / 609 (0.49%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Melaena | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Nausea | | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 4 / 609 (0.66%) | | | |
| occurrences causally related to treatment / all | 3 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pancreatitis | | | | |
| subjects affected / exposed | 2 / 609 (0.33%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Perforation gastrointestinal | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Rectal pain | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Rectal perforation | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Reflux oesophagitis | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Small bowel obstruction | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Small intestinal obstruction | | | | |
| subjects affected / exposed | 2 / 609 (0.33%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Small intestinal perforation | | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 2 / 609 (0.33%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Stagnation of intestinal contents | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subileus | | | |
| subjects affected / exposed | 11 / 609 (1.81%) | | |
| occurrences causally related to treatment / all | 3 / 11 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subocclusive syndrome | | | |
| subjects affected / exposed | 3 / 609 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper gastrointestinal hemorrhage | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 11 / 609 (1.81%) | | |
| occurrences causally related to treatment / all | 5 / 10 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Acute cholecystitis | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Autoimmune hepatitis | | | |
| subjects affected / exposed | 3 / 609 (0.49%) | | |
| occurrences causally related to treatment / all | 3 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bile duct stenosis | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 2 / 609 (0.33%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Biliary colic | | | | |
| subjects affected / exposed | 2 / 609 (0.33%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Calculus biliary | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cholestasis | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hepatic cytolysis | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gallbladder rupture | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hepatic failure | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hepatitis | | | | |
| subjects affected / exposed | 3 / 609 (0.49%) | | | |
| occurrences causally related to treatment / all | 3 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Liver disorder | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatitis acute | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatocellular injury | | | |
| subjects affected / exposed | 5 / 609 (0.82%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Cutaneous lupus erythematosus | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dermatitis | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dermatitis bullous | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dermatomyositis | | | |
| subjects affected / exposed | 2 / 609 (0.33%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Drug eruption | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Erythroderma | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Exanthema | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gallbladder perforation | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hidradenitis suppurativa | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Itching and rash | | | | |
| subjects affected / exposed | 2 / 609 (0.33%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Leg ulcer | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Macular rash | | | | |
| subjects affected / exposed | 2 / 609 (0.33%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Maculopapular rash | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Palmar-plantar erythrodysesthesia syndrome | | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin rash | | | |
| subjects affected / exposed | 21 / 609 (3.45%) | | |
| occurrences causally related to treatment / all | 19 / 21 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin toxicity | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Stevens-Johnson syndrome | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney failure | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Proteinuria | | | |
| subjects affected / exposed | 22 / 609 (3.61%) | | |
| occurrences causally related to treatment / all | 19 / 22 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute renal insufficiency | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute renal failure | | | |
| subjects affected / exposed | 5 / 609 (0.82%) | | |
| occurrences causally related to treatment / all | 2 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Glomerulonephritis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Macroscopic haematuria | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nephrotic syndrome | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pelvicaiectasis | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal failure | | | |
| subjects affected / exposed | 2 / 609 (0.33%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal insufficiency | | | |
| subjects affected / exposed | 2 / 609 (0.33%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal impairment | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocrine disorders | | | |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 2 / 609 (0.33%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Autoimmune thyroid disorder | | | |

| | | | |
|---|-------------------|--|--|
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Autoimmune thyroiditis | | | |
| subjects affected / exposed | 2 / 609 (0.33%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperthyroidism | | | |
| subjects affected / exposed | 15 / 609 (2.46%) | | |
| occurrences causally related to treatment / all | 12 / 15 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypophysitis | | | |
| subjects affected / exposed | 3 / 609 (0.49%) | | |
| occurrences causally related to treatment / all | 3 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 72 / 609 (11.82%) | | |
| occurrences causally related to treatment / all | 70 / 72 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Panhypopituitarism | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thyroiditis | | | |
| subjects affected / exposed | 2 / 609 (0.33%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 2 / 609 (0.33%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bone pain | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Joint pain | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myalgia | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myositis | | | |
| subjects affected / exposed | 4 / 609 (0.66%) | | |
| occurrences causally related to treatment / all | 4 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rhizomelic pseudopolyarthritis | | | |
| subjects affected / exposed | 2 / 609 (0.33%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Abscess | | | |
| subjects affected / exposed | 2 / 609 (0.33%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abscess dental | | | |
| subjects affected / exposed | 5 / 609 (0.82%) | | |
| occurrences causally related to treatment / all | 3 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abscess gum | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anal abscess | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 2 / 609 (0.33%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Acute upper respiratory tract infection | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ascites infection | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Aspergillosis | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bacterial sepsis | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bronchitis | | | | |
| subjects affected / exposed | 4 / 609 (0.66%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| CMV infection | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia | | | | |
| subjects affected / exposed | 6 / 609 (0.99%) | | | |
| occurrences causally related to treatment / all | 3 / 6 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| COVID-19 | | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 3 / 609 (0.49%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Device related infection | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Diverticulitis | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Encephalitis | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Enterococcus faecalis infection | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Erysipelas | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Escherichia sepsis | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Escherichia urinary tract infection | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Flu syndrome | | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infected lymphocele | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Influenza A virus infection | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| H1N1 influenza | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Groin abscess | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lower respiratory tract infection | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Papulopustular rash | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pelvic abscess | | | | |
| subjects affected / exposed | 2 / 609 (0.33%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Perianal abscess | | | | |

| | | | | |
|---|------------------|--|--|--|
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Periorbital cellulitis | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Peritoneal infection | | | | |
| subjects affected / exposed | 2 / 609 (0.33%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Peritonitis | | | | |
| subjects affected / exposed | 3 / 609 (0.49%) | | | |
| occurrences causally related to treatment / all | 3 / 3 | | | |
| deaths causally related to treatment / all | 1 / 1 | | | |
| Pyelitis | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pyelonephritis | | | | |
| subjects affected / exposed | 10 / 609 (1.64%) | | | |
| occurrences causally related to treatment / all | 0 / 10 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Respiratory infection | | | | |
| subjects affected / exposed | 2 / 609 (0.33%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Sepsis | | | | |
| subjects affected / exposed | 4 / 609 (0.66%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Septic arthritis | | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Septic shock | | | | |
| subjects affected / exposed | 2 / 609 (0.33%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Septicaemia due to Escherichia coli (E. coli) | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Stoma site infection | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Tooth abscess | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Upper respiratory infection | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Urinary infection | | | | |
| subjects affected / exposed | 8 / 609 (1.31%) | | | |
| occurrences causally related to treatment / all | 1 / 8 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Urosepsis | | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Vertebral abscess | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Arthritis bacterial | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Osteonecrosis | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diabetes | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diabetes with ketoacidosis | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Electrolyte disturbance | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperamylasemia | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypercalcemia | | | |
| subjects affected / exposed | 2 / 609 (0.33%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypercreatininaemia | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperkalemia | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperlipasemia | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypokalemia | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyponatremia | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyponatremia aggravated | | | |
| subjects affected / exposed | 1 / 609 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 2 %

| Non-serious adverse events | Safety population | | |
|---|------------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 609 / 609 (100.00%) | | |
| Vascular disorders | | | |
| HYPERTENSION | | | |
| subjects affected / exposed | 231 / 609 (37.93%) | | |
| occurrences (all) | 451 | | |
| Blood and lymphatic system disorders | | | |

| | | | |
|---|----------------------------|--|--|
| Anemia subjects affected / exposed occurrences (all) | 353 / 609 (57.96%) 1042 | | |
| NEUTROPENIA subjects affected / exposed occurrences (all) | 354 / 609 (58.13%) 1166 | | |
| THROMBOCYTOPENIA subjects affected / exposed occurrences (all) | 304 / 609 (49.92%) 1026 | | |
| LEUKOPENIA subjects affected / exposed occurrences (all) | 133 / 609 (21.84%) 416 | | |
| General disorders and administration site conditions ASTHENIA subjects affected / exposed occurrences (all) | 327 / 609 (53.69%) 817 | | |
| FATIGUE subjects affected / exposed occurrences (all) | 175 / 609 (28.74%) 377 | | |
| Gastrointestinal disorders NAUSEA subjects affected / exposed occurrences (all) | 382 / 609 (62.73%) 852 | | |
| DIARRHOEA subjects affected / exposed occurrences (all) | 239 / 609 (39.24%) 476 | | |
| CONSTIPATION subjects affected / exposed occurrences (all) | 237 / 609 (38.92%) 411 | | |
| Respiratory, thoracic and mediastinal disorders EPISTAXIS subjects affected / exposed occurrences (all) | 226 / 609 (37.11%) 326 | | |
| Renal and urinary disorders PROTEINURIA | | | |

| | | | |
|-----------------------------|--------------------|--|--|
| subjects affected / exposed | 184 / 609 (30.21%) | | |
| occurrences (all) | 480 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 04 July 2016 | Modified protocol to include clarifications of subject selection criteria. Clarification of exploratory objectives. Amended of stratification factor. Clarifications of the use of corticosteroids. Clarifications of the collection of auto-immune disease. Amended management of bevacizumab and atezolizumab specific adverse event. Modification of the frequency of questionnaires collection. Added of data sharing. |
| 20 October 2016 | Amended management of atezolizumab specific adverse event. |
| 07 April 2017 | Modified protocol to add secondary objective. Modification of statistical analysis. Clarification of inclusion criteria. |
| 18 December 2017 | Amended management of atezolizumab specific adverse events. Clarification of exclusion criteria. |
| 26 November 2018 | Increase of the number of patients (from 405 to 600), update of the study calendar, addition of a co-primary outcome, update of secondary objectives, modification of statistical methods and sample size determination, modification of the management of atezolizumab specific adverse events (addition of renal events) and suppression of PRO sub-study. |
| 17 May 2019 | Change of sponsor's address and phone number, precision regarding study treatment duration, precision of estimated date of end of study, addition of a secondary objective (PK and ADA analysis), addition of an exploratory objective, modification of statistical part, addition of a possible Blinded Independent Scan Review, precision regarding the necessity of the additional CT scan after detection of disease progression, modification of the management of atezolizumab specific adverse events (addition of immune-related Myositis), clarification regarding the unblinded treatment, clarification to make the difference between patient study treatment withdrawal and patient study withdrawal, clarification of the definition of SAE, list of AESI updated. |
| 04 May 2020 | Amended management of atezolizumab specific adverse events, list of AESI of atezolizumab updated. |
| 06 November 2020 | Modifications of statistical part and amended management of atezolizumab specific adverse events |
| 08 March 2021 | Amended management of atezolizumab specific adverse events (MAS/HLH added). |
| 26 November 2021 | Addition of secondary objective (PFS1 and OS will be evaluated according to PD-L1 and/or CD8 status) with related modifications in the chapters of Translational Research, statistical analysis and references. Alignment of the statistical test for the co-primary efficacy endpoint with Statistical Analysis Plan. Replacement of new GCIG logo and correction of minor typo. Update of the Trial Manager name. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/37643382>