



Clinical trial results:

A Randomized, Active-Controlled, Partially Blinded, Biomarker Select, Phase III Clinical Trial of Pembrolizumab as Monotherapy and in Combination with Cisplatin+5-Fluorouracil versus Placebo+Cisplatin+5-Fluorouracil as First-Line Treatment in Subjects with Advanced Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma

Summary

| | |
|--------------------------|-------------------------------------|
| EudraCT number | 2015-000972-88 |
| Trial protocol | LT DE LV NL ES CZ FR AT HU BE PL IT |
| Global end of trial date | 06 June 2022 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 05 May 2023 |
| First version publication date | 05 May 2023 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | 3475-062 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02494583 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Merck Sharp & Dohme LLC |
| Sponsor organisation address | 126 East Lincoln Avenue, P.O. Box 2000, Rahway, NJ, United States, 07065 |
| Public contact | Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.com |
| Scientific contact | Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|---------------|
| Analysis stage | Final |
| Date of interim/final analysis | 06 June 2022 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 26 March 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 06 June 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

This was a study of pembrolizumab as first-line treatment for participants with advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma. Participants whose tumors expressed programmed death-ligand 1 (PD-L1) were randomly assigned to one of the three treatment arms of the study: pembrolizumab as monotherapy [pembro mono], pembrolizumab plus standard of care (SOC) chemotherapy with cisplatin plus 5-fluorouracil (5-FU) or capecitabine [pembro combo], or placebo plus SOC chemotherapy with cisplatin plus 5-fluorouracil (5-FU) or capecitabine [SOC].

The primary hypotheses compared pembrolizumab plus SOC chemotherapy OR pembrolizumab monotherapy with SOC chemotherapy alone in terms of Progression-free Survival (PFS) and Overall Survival (OS) in participants with PD-L1 Combined Positive Score (CPS) ≥ 1 and participants with PD-L1 CPS ≥ 10 .

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 31 July 2015 |
| 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 | Argentina: 9 |
| Country: Number of subjects enrolled | Australia: 19 |
| Country: Number of subjects enrolled | Austria: 6 |
| Country: Number of subjects enrolled | Belgium: 11 |
| Country: Number of subjects enrolled | Brazil: 33 |
| Country: Number of subjects enrolled | Chile: 44 |
| Country: Number of subjects enrolled | Colombia: 11 |
| Country: Number of subjects enrolled | Czechia: 19 |
| Country: Number of subjects enrolled | Germany: 19 |
| Country: Number of subjects enrolled | Guatemala: 22 |
| Country: Number of subjects enrolled | Hong Kong: 7 |
| Country: Number of subjects enrolled | Hungary: 28 |
| Country: Number of subjects enrolled | Italy: 22 |
| Country: Number of subjects enrolled | Japan: 103 |

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Korea, Republic of: 50 |
| Country: Number of subjects enrolled | Latvia: 23 |
| Country: Number of subjects enrolled | Lithuania: 14 |
| Country: Number of subjects enrolled | Mexico: 14 |
| Country: Number of subjects enrolled | Netherlands: 7 |
| Country: Number of subjects enrolled | New Zealand: 3 |
| Country: Number of subjects enrolled | Poland: 44 |
| Country: Number of subjects enrolled | Russian Federation: 64 |
| Country: Number of subjects enrolled | South Africa: 21 |
| Country: Number of subjects enrolled | Spain: 34 |
| Country: Number of subjects enrolled | Switzerland: 15 |
| Country: Number of subjects enrolled | Taiwan: 27 |
| Country: Number of subjects enrolled | United Kingdom: 25 |
| Country: Number of subjects enrolled | United States: 69 |
| Worldwide total number of subjects | 763 |
| EEA total number of subjects | 227 |

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) | 445 |
| From 65 to 84 years | 315 |
| 85 years and over | 3 |

Subject disposition

Recruitment

Recruitment details:

Participants with advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma who were programmed death-ligand 1 (PD-L1)-positive (Combined Positive Score [CPS] ≥ 1) and human epidermal growth factor receptor 2 (HER2/neu)-negative were recruited to the study.

Pre-assignment

Screening details:

763 were randomized 1:1:1 to pembrolizumab monotherapy (pembro mono), pembrolizumab plus standard of care (SOC) chemotherapy (pembro combo), or placebo plus SOC. Per protocol, response/progression or adverse events (AEs) occurring during second course not counted towards efficacy outcome measures or safety outcome measures, respectively.

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, Carer, Assessor |

Blinding implementation details:

For pembrolizumab (monotherapy); the participant, the trial site personnel, the Sponsor and/or designee were not blinded to this treatment arm since only one type of trial medication was administered on this arm.

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | Yes |
| Arm title | Pembrolizumab Monotherapy (Pembro Mono) |

Arm description:

Participants received pembrolizumab 200 mg intravenously (IV) on Day 1 of each 3-week cycle (Q3W). Eligible participants who stopped the initial course of pembrolizumab with Stable Disease (SD) or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab for up to 17 cycles (up to approximately 1 additional year) at the investigator's discretion.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Pembrolizumab |
| Investigational medicinal product code | |
| Other name | KEYTRUDA®, MK-3475 |
| Pharmaceutical forms | Concentrate and solvent for concentrate for solution for infusion, Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

200 mg/kg IV, administered Q3W

| | |
|------------------|---|
| Arm title | Pembrolizumab + SOC Chemotherapy (Pembro Combo) |
|------------------|---|

Arm description:

Participants received pembrolizumab 200 mg Q3W plus cisplatin 80 mg/m² Q3W plus 5-fluorouracil (5-FU) 800 mg/m²/day IV infusion on Days 1-5 Q3W. Capecitabine 1000 mg/m² twice a day (BID) on Days 1-14 Q3W could be substituted for 5-FU per local guidelines. Eligible participants who stopped the initial course of pembrolizumab with Stable Disease (SD) or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab for up to 17 cycles (up to approximately 1 additional year) at the investigator's discretion.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|---|--|
| Investigational medicinal product name | Pembrolizumab |
| Investigational medicinal product code | |
| Other name | KEYTRUDA®, MK-3475 |
| Pharmaceutical forms | Concentrate and solvent for concentrate for solution for infusion, Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: 200 mg/kg IV, administered Q3W | |
| Investigational medicinal product name | Capecitabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: Capecitabine 1000 mg/m ² twice daily by oral tablet on Day 1-14 of each 3-week cycle. | |
| Investigational medicinal product name | 5-FU |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: 5-FU 800 mg/m ² /day IV continuous from Day 1-5 of each 3-week cycle. | |
| Investigational medicinal product name | Cisplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: 80 mg/m ² IV on Day 1 of each week in 3-week cycles (6 cycle maximum per local country guidelines). | |
| Arm title | Placebo + SOC Chemotherapy (SOC) |
| Arm description: Participants received placebo IV Q3W plus cisplatin 80 mg/m ² Q3W plus 5-FU 800 mg/m ² /day IV infusion on Days 1-5 Q3W. Capecitabine 1000 mg/m ² BID on Days 1-14 Q3W could be substituted for 5-FU per local guidelines. | |
| Arm type | Experimental |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: Normal saline IV on Day 1 of each week in 3-week cycles for up to 35 cycles (approximately 2 years). | |
| Investigational medicinal product name | Capecitabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: Capecitabine 1000 mg/m ² twice daily by oral tablet on Day 1-14 of each 3-week cycle. | |
| Investigational medicinal product name | 5-FU |
| Investigational medicinal product code | |
| Other name | |

| | |
|--|-----------------------|
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 5-FU 800 mg/m ² /day IV continuous from Day 1-5 of each 3-week cycle. | |
| Investigational medicinal product name | Cisplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 80 mg/m ² IV on Day 1 of each week in 3-week cycles (6 cycle maximum per local country guidelines). | |

| Number of subjects in period 1 | Pembrolizumab Monotherapy (Pembro Mono) | Pembrolizumab + SOC Chemotherapy (Pembro Combo) | Placebo + SOC Chemotherapy (SOC) |
|---|---|---|----------------------------------|
| Started | 256 | 257 | 250 |
| Received First Course of Pembrolizumab | 254 | 250 | 244 |
| Received Second Course of Pembrolizumab | 4 | 5 | 0 |
| Completed | 0 | 0 | 0 |
| Not completed | 256 | 257 | 250 |
| Consent withdrawn by subject | 7 | 15 | 15 |
| Screen Failure | - | 1 | - |
| Transferred to Extension Study | 15 | 15 | 6 |
| Death | 224 | 214 | 225 |
| Lost to follow-up | 1 | - | - |
| Did Not Continue on Extension Study | 8 | 10 | 4 |
| Protocol deviation | 1 | 2 | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | Pembrolizumab Monotherapy (Pembro Mono) |
|-----------------------|---|

Reporting group description:

Participants received pembrolizumab 200 mg intravenously (IV) on Day 1 of each 3-week cycle (Q3W). Eligible participants who stopped the initial course of pembrolizumab with Stable Disease (SD) or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab for up to 17 cycles (up to approximately 1 additional year) at the investigator's discretion.

| | |
|-----------------------|---|
| Reporting group title | Pembrolizumab + SOC Chemotherapy (Pembro Combo) |
|-----------------------|---|

Reporting group description:

Participants received pembrolizumab 200 mg Q3W plus cisplatin 80 mg/m² Q3W plus 5-fluorouracil (5-FU) 800 mg/m²/day IV infusion on Days 1-5 Q3W. Capecitabine 1000 mg/m² twice a day (BID) on Days 1-14 Q3W could be substituted for 5-FU per local guidelines. Eligible participants who stopped the initial course of pembrolizumab with Stable Disease (SD) or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab for up to 17 cycles (up to approximately 1 additional year) at the investigator's discretion.

| | |
|-----------------------|----------------------------------|
| Reporting group title | Placebo + SOC Chemotherapy (SOC) |
|-----------------------|----------------------------------|

Reporting group description:

Participants received placebo IV Q3W plus cisplatin 80 mg/m² Q3W plus 5-FU 800 mg/m²/day IV infusion on Days 1-5 Q3W. Capecitabine 1000 mg/m² BID on Days 1-14 Q3W could be substituted for 5-FU per local guidelines.

| Reporting group values | Pembrolizumab Monotherapy (Pembro Mono) | Pembrolizumab + SOC Chemotherapy (Pembro Combo) | Placebo + SOC Chemotherapy (SOC) |
|---|---|---|----------------------------------|
| Number of subjects | 256 | 257 | 250 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 154 | 152 | 139 |
| From 65-84 years | 102 | 105 | 108 |
| 85 years and over | 0 | 0 | 3 |
| Age Continuous Units: Years | | | |
| arithmetic mean | 59.9 | 60.9 | 60.7 |
| standard deviation | ± 11.6 | ± 11.6 | ± 12.7 |
| Sex: Female, Male Units: Participants | | | |
| Female | 76 | 62 | 71 |
| Male | 180 | 195 | 179 |
| Race (NIH/OMB) Units: Subjects | | | |
| American Indian or Alaska Native | 9 | 7 | 13 |
| Asian | 69 | 71 | 67 |
| Native Hawaiian or Other Pacific Islander | 1 | 0 | 1 |
| Black or African American | 4 | 4 | 5 |
| White | 164 | 167 | 154 |
| More than one race | 9 | 6 | 7 |
| Unknown or Not Reported | 0 | 2 | 3 |
| Ethnicity (NIH/OMB) Units: Subjects | | | |
| Hispanic or Latino | 45 | 54 | 46 |

| | | | |
|--|-----|-----|-----|
| Not Hispanic or Latino | 206 | 196 | 197 |
| Unknown or Not Reported | 5 | 7 | 7 |
| Region of Enrollment | | | |
| Participants were stratified according to geographic region of enrolling site: Europe (including Israel)/North America/Australia, Asia (including East Asia [South Korea, Hong Kong, Taiwan], South East Asia [Malaysia], Thailand, Singapore, Japan), or Rest of the World (including South America). | | | |
| Units: Subjects | | | |
| Europe/North America/Australia | 148 | 148 | 147 |
| Asia | 62 | 64 | 61 |
| Rest of the World | 46 | 45 | 42 |
| Disease Status | | | |
| Participants were stratified according to gastric cancer disease status as either locally advanced unresectable or metastatic disease. | | | |
| Units: Subjects | | | |
| Locally advanced | 10 | 12 | 13 |
| Metastatic | 245 | 243 | 235 |
| Missing | 1 | 2 | 2 |
| Fluoropyrimidine Treatment | | | |
| Participants receiving SOC chemotherapy were stratified according to fluoropyrimidine treatment (5-FU or capecitabine). | | | |
| Units: Subjects | | | |
| 5-FU | 97 | 98 | 95 |
| Capecitabine | 159 | 159 | 155 |

| | | | |
|---|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 763 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 445 | | |
| From 65-84 years | 315 | | |
| 85 years and over | 3 | | |
| Age Continuous | | | |
| Units: Years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Sex: Female, Male | | | |
| Units: Participants | | | |
| Female | 209 | | |
| Male | 554 | | |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 29 | | |
| Asian | 207 | | |
| Native Hawaiian or Other Pacific Islander | 2 | | |
| Black or African American | 13 | | |
| White | 485 | | |
| More than one race | 22 | | |
| Unknown or Not Reported | 5 | | |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 145 | | |
| Not Hispanic or Latino | 599 | | |

| | | | |
|--|-----|--|--|
| Unknown or Not Reported | 19 | | |
| Region of Enrollment | | | |
| Participants were stratified according to geographic region of enrolling site: Europe (including Israel)/North America/Australia, Asia (including East Asia [South Korea, Hong Kong, Taiwan], South East Asia [Malaysia], Thailand, Singapore, Japan), or Rest of the World (including South America). | | | |
| Units: Subjects | | | |
| Europe/North America/Australia | 443 | | |
| Asia | 187 | | |
| Rest of the World | 133 | | |
| Disease Status | | | |
| Participants were stratified according to gastric cancer disease status as either locally advanced unresectable or metastatic disease. | | | |
| Units: Subjects | | | |
| Locally advanced | 35 | | |
| Metastatic | 723 | | |
| Missing | 5 | | |
| Fluoropyrimidine Treatment | | | |
| Participants receiving SOC chemotherapy were stratified according to fluoropyrimidine treatment (5-FU or capecitabine). | | | |
| Units: Subjects | | | |
| 5-FU | 290 | | |
| Capecitabine | 473 | | |

End points

End points reporting groups

| | |
|--|---|
| Reporting group title | Pembrolizumab Monotherapy (Pembro Mono) |
| Reporting group description: Participants received pembrolizumab 200 mg intravenously (IV) on Day 1 of each 3-week cycle (Q3W). Eligible participants who stopped the initial course of pembrolizumab with Stable Disease (SD) or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab for up to 17 cycles (up to approximately 1 additional year) at the investigator's discretion. | |
| Reporting group title | Pembrolizumab + SOC Chemotherapy (Pembro Combo) |
| Reporting group description: Participants received pembrolizumab 200 mg Q3W plus cisplatin 80 mg/m ² Q3W plus 5-fluorouracil (5-FU) 800 mg/m ² /day IV infusion on Days 1-5 Q3W. Capecitabine 1000 mg/m ² twice a day (BID) on Days 1-14 Q3W could be substituted for 5-FU per local guidelines. Eligible participants who stopped the initial course of pembrolizumab with Stable Disease (SD) or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab for up to 17 cycles (up to approximately 1 additional year) at the investigator's discretion. | |
| Reporting group title | Placebo + SOC Chemotherapy (SOC) |
| Reporting group description: Participants received placebo IV Q3W plus cisplatin 80 mg/m ² Q3W plus 5-FU 800 mg/m ² /day IV infusion on Days 1-5 Q3W. Capecitabine 1000 mg/m ² BID on Days 1-14 Q3W could be substituted for 5-FU per local guidelines. | |

Primary: Pembro Combo vs SOC: Progression Free Survival (PFS) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) by Blinded Independent Central Review (BICR) in Participants With PD-L1 CPS ≥1 (All Participants)

| | |
|-----------------|--|
| End point title | Pembro Combo vs SOC: Progression Free Survival (PFS) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) by Blinded Independent Central Review (BICR) in Participants With PD-L1 CPS ≥1 (All Participants) |
|-----------------|--|

End point description:

PFS was defined as the time from randomization to the first documented progressive disease (PD) per RECIST 1.1 based on BICR, or death due to any cause, whichever occurred first. Per RECIST 1.1, PD was defined as ≥20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum had to demonstrate an absolute increase of ≥5 mm. The appearance of one or more new lesions was also considered PD.

Per protocol, PFS in the pembro combo arm was compared to the SOC arm as a pre-specified primary analysis of the Intent-To-Treat (ITT) population. PFS is reported here for all participants in the pembro combo arm and SOC arm who were PD-L1 CPS ≥1 (all participants). Per protocol, PFS was compared separately between CPS ≥1 participants of the pembro mono arm and SOC arm and is presented later in the record.

All CPS ≥1 participants in the ITT population randomized to the pembro combo arm and SOC arm were analyzed.

| | |
|---|---------|
| End point type | Primary |
| End point timeframe: Up to approximately 36 months | |

| End point values | Pembrolizumab Monotherapy (Pembro Mono) | Pembrolizumab + SOC Chemotherapy (Pembro Combo) | Placebo + SOC Chemotherapy (SOC) | |
|----------------------------------|---|---|----------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0 ^[1] | 257 | 250 | |
| Units: Months | | | | |
| median (confidence interval 95%) | (to) | 6.9 (5.7 to 7.3) | 6.4 (5.7 to 7.0) | |

Notes:

[1] - The pembro mono arm was compared to the SOC arm separately and not included in this analysis.

Statistical analyses

| | |
|---|--|
| Statistical analysis title | PFS: Pembro Combo vs SOC, CPS ≥ 1 |
| Statistical analysis description: | |
| PFS in CPS ≥ 1 participants of the pembro combo arm was compared to PFS in CPS ≥ 1 participants of the SOC arm to address the first primary hypothesis (superiority to SOC). The comparison was based on a Cox regression model with Efron's method of tie handling with treatment as a covariate with stratification according to geographic region, disease status, and fluoropyrimidine treatment. | |
| Comparison groups | Pembrolizumab + SOC Chemotherapy (Pembro Combo) v Placebo + SOC Chemotherapy (SOC) |
| Number of subjects included in analysis | 507 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.03918 ^[2] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.84 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.7 |
| upper limit | 1.02 |

Notes:

[2] - One-sided p-value based on log-rank test with stratification.

Primary: Pembro Combo vs SOC: Overall Survival (OS) in Participants With PD-L1 CPS ≥ 1 (All Participants)

| | |
|--|---|
| End point title | Pembro Combo vs SOC: Overall Survival (OS) in Participants With PD-L1 CPS ≥ 1 (All Participants) |
| End point description: | |
| OS was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the final analysis were censored at the date of the last follow-up. Per protocol, OS in the pembro combo arm was compared to the SOC arm as a pre-specified primary analysis of the ITT population. OS is reported here for all participants in the pembro combo arm and SOC arm who were PD-L1 CPS ≥ 1 (all participants). Per protocol, OS was compared separately between CPS ≥ 1 participants of the pembro mono arm and SOC arm and is presented later in the record. All CPS ≥ 1 participants in the ITT population randomized to the pembro combo arm and SOC arm were analyzed. | |
| End point type | Primary |
| End point timeframe: | |
| Up to approximately 42 months | |

| End point values | Pembrolizumab Monotherapy (Pembro Mono) | Pembrolizumab + SOC Chemotherapy (Pembro Combo) | Placebo + SOC Chemotherapy (SOC) | |
|----------------------------------|---|---|----------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0 ^[3] | 257 | 250 | |
| Units: Months | | | | |
| median (confidence interval 95%) | (to) | 12.5 (10.8 to 13.9) | 11.1 (9.2 to 12.8) | |

Notes:

[3] - The pembro mono arm was compared to the SOC arm separately and not included in this analysis.

Statistical analyses

| | |
|--|--|
| Statistical analysis title | OS: Pembro Combo vs SOC, CPS ≥ 1 |
| Statistical analysis description: | |
| OS in CPS ≥ 1 participants of the pembro combo arm was compared to OS in CPS ≥ 1 participants of the SOC arm to address the second primary hypothesis (superiority to SOC). The comparison was based on a Cox regression model with Efron's method of tie handling with treatment as a covariate with stratification according to geographic region, disease status, and Fluoropyrimidine treatment. | |
| Comparison groups | Pembrolizumab + SOC Chemotherapy (Pembro Combo) v Placebo + SOC Chemotherapy (SOC) |
| Number of subjects included in analysis | 507 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.04611 ^[4] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.85 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.7 |
| upper limit | 1.03 |

Notes:

[4] - One-sided p-value based on log-rank test with stratification.

Primary: Pembro Combo vs SOC: OS in Participants With PD-L1 CPS ≥ 10

| | |
|---|--|
| End point title | Pembro Combo vs SOC: OS in Participants With PD-L1 CPS ≥ 10 |
| End point description: | |
| OS was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the final analysis were censored at the date of the last follow-up. Per protocol, OS in the pembro combo arm was compared to the SOC arm as a pre-specified primary analysis of the ITT population. OS is reported here for all participants in the pembro combo arm and SOC arm who were PD-L1 CPS ≥ 10 . Per protocol, OS was compared separately between CPS ≥ 10 participants of the pembro mono arm and SOC arm and is presented later in the record. All CPS ≥ 10 participants in the ITT population randomized to the pembro combo arm and SOC arm were analyzed. | |
| End point type | Primary |
| End point timeframe: | |
| Up to approximately 42 months | |

| End point values | Pembrolizumab Monotherapy (Pembro Mono) | Pembrolizumab + SOC Chemotherapy (Pembro Combo) | Placebo + SOC Chemotherapy (SOC) | |
|----------------------------------|---|---|----------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0 ^[5] | 99 | 90 | |
| Units: Months | | | | |
| median (confidence interval 95%) | (to) | 12.3 (9.5 to 14.8) | 10.8 (8.5 to 13.8) | |

Notes:

[5] - The pembro mono arm was compared to the SOC arm separately and not included in this analysis.

Statistical analyses

| | |
|---|--|
| Statistical analysis title | OS: Pembro Combo vs SOC, CPS ≥ 10 |
| Statistical analysis description: | |
| OS in CPS ≥ 10 participants of the pembro combo arm was compared to OS in CPS ≥ 10 participants of the SOC arm to address the third primary hypothesis (superiority to SOC). The comparison was based on a Cox regression model with Efron's method of tie handling with treatment as a covariate with stratification according to geographic region, disease status, and Fluoropyrimidine treatment. | |
| Comparison groups | Pembrolizumab + SOC Chemotherapy (Pembro Combo) v Placebo + SOC Chemotherapy (SOC) |
| Number of subjects included in analysis | 189 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.15804 ^[6] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.85 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.62 |
| upper limit | 1.17 |

Notes:

[6] - One-sided p-value based on log-rank test with stratification.

Primary: Pembro Mono vs SOC: OS in Participants With PD-L1 CPS ≥ 1 (All Participants)

| | |
|--|---|
| End point title | Pembro Mono vs SOC: OS in Participants With PD-L1 CPS ≥ 1 (All Participants) |
| End point description: | |
| OS was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the final analysis were censored at the date of the last follow-up. Per protocol, OS in the pembro mono arm was compared to the SOC arm as a pre-specified primary analysis of the ITT population. OS is reported here for all participants in the pembro mono arm and SOC arm who were PD-L1 CPS ≥ 1 (all participants). Per protocol, OS was compared separately between CPS ≥ 1 participants of the pembro combo arm and SOC arm and is presented earlier in the record. All CPS ≥ 1 participants in the ITT population randomized to the pembro mono arm and SOC arm were analyzed. | |
| End point type | Primary |

End point timeframe:
Up to approximately 42 months

| End point values | Pembrolizumab Monotherapy (Pembro Mono) | Pembrolizumab + SOC Chemotherapy (Pembro Combo) | Placebo + SOC Chemotherapy (SOC) | |
|----------------------------------|---|---|----------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 256 | 0 ^[7] | 250 | |
| Units: Months | | | | |
| median (confidence interval 95%) | 10.6 (7.7 to 13.8) | (to) | 11.1 (9.2 to 12.8) | |

Notes:

[7] - The pembro combo arm was compared to the SOC arm separately and not included in this analysis.

Statistical analyses

| Statistical analysis title | OS non-inferiority: Pembro Mono vs SOC, CPS ≥ 1 |
|---|--|
| Statistical analysis description: | |
| OS in CPS ≥ 1 participants of the pembro mono arm was compared to OS in CPS ≥ 1 participants of the SOC arm to address the fourth primary hypothesis (non-inferiority to SOC). The comparison was based on a Cox regression model with Efron's method of tie handling with treatment as a covariate with stratification according to geographic region, disease status, and Fluoropyrimidine treatment. | |
| Comparison groups | Pembrolizumab Monotherapy (Pembro Mono) v Placebo + SOC Chemotherapy (SOC) |
| Number of subjects included in analysis | 506 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.91 |
| Confidence interval | |
| level | Other: 99.2 % |
| sides | 2-sided |
| lower limit | 0.69 |
| upper limit | 1.18 |

| Statistical analysis title | OS superiority: Pembro Mono vs SOC, CPS ≥ 1 |
|--|--|
| Statistical analysis description: | |
| OS in CPS ≥ 1 participants of the pembro mono arm was compared to OS in CPS ≥ 1 participants of the SOC arm to address the fifth primary hypothesis (superiority to SOC). The comparison was based on a Cox regression model with Efron's method of tie handling with treatment as a covariate with stratification according to geographic region, disease status, and Fluoropyrimidine treatment. | |
| Comparison groups | Pembrolizumab Monotherapy (Pembro Mono) v Placebo + SOC Chemotherapy (SOC) |

| | |
|---|--------------------------|
| Number of subjects included in analysis | 506 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.16205 ^[8] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.91 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.74 |
| upper limit | 1.1 |

Notes:

[8] - One-sided p-value based on log-rank test with stratification.

Primary: Pembro Mono vs SOC: OS in Participants With PD-L1 CPS ≥10

| | |
|-----------------|---|
| End point title | Pembro Mono vs SOC: OS in Participants With PD-L1 CPS ≥10 |
|-----------------|---|

End point description:

OS was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the final analysis were censored at the date of the last follow-up. Per protocol, OS in the pembro mono arm was compared to the SOC arm as a pre-specified primary analysis of the ITT population. OS is reported here for all participants in the pembro mono arm and SOC arm who were PD-L1 CPS ≥10. Per protocol, OS was compared separately between CPS ≥10 participants of the pembro combo arm and SOC arm and is presented earlier in the record. All CPS ≥10 participants in the ITT population randomized to the pembro mono arm and SOC arm were analyzed.

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

End point timeframe:

Up to approximately 42 months

| End point values | Pembrolizumab Monotherapy (Pembro Mono) | Pembrolizumab + SOC Chemotherapy (Pembro Combo) | Placebo + SOC Chemotherapy (SOC) | |
|----------------------------------|---|---|----------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 92 | 0 ^[9] | 90 | |
| Units: Months | | | | |
| median (confidence interval 95%) | 17.4 (9.1 to 23.1) | (to) | 10.8 (8.5 to 13.8) | |

Notes:

[9] - The pembro combo arm was compared to the SOC arm separately and not included in this analysis.

Statistical analyses

| | |
|----------------------------|---------------------------------|
| Statistical analysis title | OS: Pembro Mono vs SOC, CPS ≥10 |
|----------------------------|---------------------------------|

Statistical analysis description:

OS in CPS ≥10 participants of the pembro mono arm was compared to OS in CPS ≥10 participants of the SOC arm to address the sixth primary hypothesis (superiority to SOC). The comparison was based on a Cox regression model with Efron's method of tie handling with treatment as a covariate with stratification according to geographic region, disease status, and Fluoropyrimidine treatment.

| | |
|-------------------|--|
| Comparison groups | Pembrolizumab Monotherapy (Pembro Mono) v Placebo + SOC Chemotherapy (SOC) |
|-------------------|--|

| | |
|---|---------------------------|
| Number of subjects included in analysis | 182 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.01491 ^[10] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.69 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.49 |
| upper limit | 0.97 |

Notes:

[10] - One-sided p-value based on log-rank test with stratification.

Secondary: Pembro Combo vs SOC: Objective Response Rate (ORR) per RECIST 1.1 by BICR in Participants With PD-L1 CPS ≥1 (All Participants)

| | |
|-----------------|--|
| End point title | Pembro Combo vs SOC: Objective Response Rate (ORR) per RECIST 1.1 by BICR in Participants With PD-L1 CPS ≥1 (All Participants) |
|-----------------|--|

End point description:

ORR was defined as the percentage of participants in the analysis population who have a Complete Response (CR: disappearance of all target lesions) or a Partial Response (PR: ≥30% decrease in the sum of diameters of target lesions) per RECIST 1.1. based upon BICR. Per protocol, ORR in the pembro combo arm was compared to the SOC arm as a pre-specified secondary analysis of the ITT population. The percentage of participants who experienced CR or PR is reported here as the ORR for all participants in the pembro combo arm and SOC arm who were PD-L1 CPS ≥1 (all participants). Per protocol, ORR was compared separately between CPS ≥1 participants of the pembro mono arm and SOC arm and is presented later in the record. All CPS ≥1 participants in the ITT population randomized to the pembro combo arm and SOC arm were analyzed.

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

End point timeframe:

Up to approximately 42 months

| End point values | Pembrolizumab Monotherapy (Pembro Mono) | Pembrolizumab + SOC Chemotherapy (Pembro Combo) | Placebo + SOC Chemotherapy (SOC) | |
|-----------------------------------|---|---|----------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0 ^[11] | 257 | 250 | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | (to) | 48.6 (42.4 to 54.9) | 37.2 (31.2 to 43.5) | |

Notes:

[11] - The pembro mono arm was compared to the SOC arm separately and not included in this analysis.

Statistical analyses

| | |
|----------------------------|----------------------------------|
| Statistical analysis title | ORR: Pembro Combo vs SOC, CPS ≥1 |
|----------------------------|----------------------------------|

Statistical analysis description:

ORR in CPS ≥1 participants of the pembro combo arm was compared to ORR in CPS ≥1 participants of the SOC arm based on Miettinen & Nurminen method stratified by geographic region, disease status,

and Fluoropyrimidine treatment.

| | |
|---|--|
| Comparison groups | Pembrolizumab + SOC Chemotherapy (Pembro Combo) v Placebo + SOC Chemotherapy (SOC) |
| Number of subjects included in analysis | 507 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.00447 ^[12] |
| Method | Miettinen & Nurminen method |
| Parameter estimate | Difference in ORR Percentage |
| Point estimate | 11.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.9 |
| upper limit | 20 |

Notes:

[12] - No formal hypothesis testing performed; nominal p-value provided for treatment comparison.

Secondary: Pembro Combo vs SOC: Duration of Response (DOR) per RECIST 1.1 by BICR in Participants With PD-L1 CPS ≥1 (All Participants)

| | |
|-----------------|---|
| End point title | Pembro Combo vs SOC: Duration of Response (DOR) per RECIST 1.1 by BICR in Participants With PD-L1 CPS ≥1 (All Participants) |
|-----------------|---|

End point description:

DOR was defined as the time from first documented evidence of confirmed CR or PR until PD or death, whichever occurred first. DOR for participants who had not progressed or died at the time of analysis was censored at the date of their last tumor assessment. Per RECIST 1.1, PD was defined as at least a 20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum had to demonstrate an absolute increase of ≥5 mm. The appearance of one or more new lesions was also considered PD. All CPS ≥1 participants in the ITT population randomized to the pembro combo arm and SOC arm and who demonstrated a confirmed CR or PR were analyzed. Values of 9999 indicate that the median DOR and DOR range lower and upper limits were not reached (no progressive disease by time of last disease assessment). Per protocol, DOR was compared separately between CPS ≥1 responders of the pembro mono arm and SOC arm and is presented later in the record.

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

End point timeframe:

Up to approximately 42 months

| End point values | Pembrolizumab Monotherapy (Pembro Mono) | Pembrolizumab + SOC Chemotherapy (Pembro Combo) | Placebo + SOC Chemotherapy (SOC) | |
|-------------------------------|---|---|----------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0 ^[13] | 125 | 93 | |
| Units: Months | | | | |
| median (full range (min-max)) | (to) | 9999 (9999 to 9999) | 9999 (9999 to 9999) | |

Notes:

[13] - The pembro mono arm was compared to the SOC arm separately and not included in this analysis.

Statistical analyses

Secondary: Pembro Mono vs SOC: ORR per RECIST 1.1 by BICR in Participants With PD-L1 CPS ≥1 (All Participants)

| | |
|---|---|
| End point title | Pembro Mono vs SOC: ORR per RECIST 1.1 by BICR in Participants With PD-L1 CPS ≥1 (All Participants) |
| End point description: | |
| <p>ORR was defined as the percentage of participants in the analysis population who have a CR (disappearance of all target lesions) or PR (≥30% decrease in the sum of diameters of target lesions) per RECIST 1.1, based upon BICR. Per protocol, ORR in the pembro mono arm was compared to the SOC arm as a pre-specified secondary analysis of the ITT population. The percentage of participants who experienced CR or PR is reported here as the ORR for all participants in the pembro mono arm and SOC arm who were PD-L1 CPS ≥1 (all participants). Per protocol, ORR was compared separately between CPS ≥1 participants of the pembro combo arm and SOC arm and is presented earlier in the record. All CPS ≥1 participants in the ITT population randomized to the pembro mono arm and SOC arm were analyzed.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| Up to approximately 42 months | |

| End point values | Pembrolizumab Monotherapy (Pembro Mono) | Pembrolizumab + SOC Chemotherapy (Pembro Combo) | Placebo + SOC Chemotherapy (SOC) | |
|-----------------------------------|---|---|----------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 256 | 0 ^[14] | 250 | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 14.8 (10.7 to 19.8) | (to) | 37.2 (31.2 to 43.5) | |

Notes:

[14] - The pembro combo arm was compared to the SOC arm separately and not included in this analysis.

Statistical analyses

| | |
|--|--|
| Statistical analysis title | ORR: Pembro Mono vs SOC, CPS ≥1 |
| Statistical analysis description: | |
| <p>ORR in CPS ≥1 participants of the pembro mono arm was compared to ORR in CPS ≥1 participants of the SOC arm based on Miettinen & Nurminen method stratified by geographic region, disease status, and Fluoropyrimidine treatment.</p> | |
| Comparison groups | Pembrolizumab Monotherapy (Pembro Mono) v Placebo + SOC Chemotherapy (SOC) |
| Number of subjects included in analysis | 506 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | > 0.99999 ^[15] |
| Method | Miettinen & Nurminen method |
| Parameter estimate | Difference in ORR Percentage |
| Point estimate | -22.3 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -29.6 |
| upper limit | -14.9 |

Notes:

[15] - No formal hypothesis testing performed; nominal p-value provided for treatment comparison.

Secondary: Pembro Mono vs SOC: DOR per RECIST 1.1 by BICR in Participants With PD-L1 CPS ≥1 (All Participants)

| | |
|-----------------|---|
| End point title | Pembro Mono vs SOC: DOR per RECIST 1.1 by BICR in Participants With PD-L1 CPS ≥1 (All Participants) |
|-----------------|---|

End point description:

DOR was defined as the time from first documented evidence of confirmed CR or PR until PD or death, whichever occurred first. DOR for participants who had not progressed or died at the time of analysis was censored at the date of their last tumor assessment. Per RECIST 1.1, PD was defined as at least a 20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum had to demonstrate an absolute increase of ≥5 mm. The appearance of one or more new lesions was also considered PD. All CPS ≥1 participants in the ITT population randomized to the pembro mono arm and SOC arm and who demonstrated a confirmed CR or PR were analyzed. Values of 9999 indicate that the median DOR and DOR range lower and upper limits were not reached (no progressive disease by time of last disease assessment). Per protocol, DOR was compared separately between CPS ≥1 responders of the pembro combo arm and SOC arm and is presented earlier in the record.

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

End point timeframe:

Up to approximately 42 months

| End point values | Pembrolizumab Monotherapy (Pembro Mono) | Pembrolizumab + SOC Chemotherapy (Pembro Combo) | Placebo + SOC Chemotherapy (SOC) | |
|-------------------------------|---|---|----------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 38 | 0 ^[16] | 93 | |
| Units: Months | | | | |
| median (full range (min-max)) | 9999 (9999 to 9999) | (to) | 9999 (9999 to 9999) | |

Notes:

[16] - The pembro combo arm was compared to the SOC arm separately and not included in this analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Pembro Mono vs SOC: PFS per RECIST 1.1 by BICR in Participants With PD-L1 CPS ≥1 (All Participants)

| | |
|-----------------|---|
| End point title | Pembro Mono vs SOC: PFS per RECIST 1.1 by BICR in Participants With PD-L1 CPS ≥1 (All Participants) |
|-----------------|---|

End point description:

PFS was defined as the time from randomization to the first documented PD per RECIST 1.1 based on BICR, or death due to any cause, whichever occurred first. Per RECIST 1.1, PD was defined as ≥20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum had to demonstrate an absolute increase of ≥5 mm. The appearance of one or more new lesions was also considered PD.

Per protocol, PFS in the pembro mono arm was compared to the SOC arm as a pre-specified secondary analysis of the ITT population. PFS is reported here for all participants in the pembro mono arm and SOC arm who were PD-L1 CPS ≥ 1 (all participants). Per protocol, PFS was compared separately between CPS ≥ 1 participants of the pembro combo arm and SOC arm and is presented earlier in the record. All CPS ≥ 1 participants in the ITT population randomized to the pembro mono arm and SOC arm were analyzed.

| | |
|-------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to approximately 42 months | |

| End point values | Pembrolizumab Monotherapy (Pembro Mono) | Pembrolizumab + SOC Chemotherapy (Pembro Combo) | Placebo + SOC Chemotherapy (SOC) | |
|----------------------------------|---|---|----------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 256 | 0 ^[17] | 250 | |
| Units: Months | | | | |
| median (confidence interval 95%) | 2.0 (1.5 to 2.8) | (to) | 6.4 (5.7 to 7.1) | |

Notes:

[17] - The pembro combo arm was compared to the SOC arm separately and not included in this analysis.

Statistical analyses

| | |
|-----------------------------------|---------------------------------------|
| Statistical analysis title | ORR: Pembro Mono vs SOC, CPS ≥ 1 |
|-----------------------------------|---------------------------------------|

Statistical analysis description:

PFS in CPS ≥ 1 participants of the pembro mono arm was compared to PFS in CPS ≥ 1 participants of the SOC arm based on a Cox regression model with Efron's method of tie handling with treatment as a covariate with stratification according to geographic region, disease status, and fluoropyrimidine treatment.

| | |
|---|--|
| Comparison groups | Pembrolizumab Monotherapy (Pembro Mono) v Placebo + SOC Chemotherapy (SOC) |
| Number of subjects included in analysis | 506 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 1 ^[18] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.64 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.36 |
| upper limit | 1.98 |

Notes:

[18] - No formal hypothesis testing performed; nominal p-value provided for treatment comparison.

Secondary: Pembro Mono vs SOC: Change from Baseline to Week 18 in the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) Global Health Status/Quality of Life (Items 29 and 30) Combined Score

| | |
|--|---|
| End point title | Pembro Mono vs SOC: Change from Baseline to Week 18 in the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) Global Health Status/Quality of Life (Items 29 and 30) Combined Score |
| End point description: | |
| <p>The EORTC-QLQ-C30 is a 30-item questionnaire developed to assess the quality of life of cancer patients. Participant responses to the Global Health Status (GHS) question "How would you rate your overall health during the past week?" (Item 29) and the Quality of Life (QoL) question "How would you rate your overall quality of life during the past week?" (Item 30) were scored on a 7-point scale (1=Very Poor to 7=Excellent). Using linear transformation, raw scores were standardized so that scores ranged from 0 to 100, with a higher score indicating a better overall outcome. Participants in the pembro mono arm and SOC arm who received ≥ 1 dose of study drug and who had EORTC-QLQ-C30 assessments available at baseline or post-baseline up to Week 18 were analyzed. Per protocol, change from baseline to Week 18 in the GHS/QoL combined score was compared separately between all participants of the pembro combo arm and SOC arm and is presented later in the record.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 18 | |

| End point values | Pembrolizumab Monotherapy (Pembro Mono) | Pembrolizumab + SOC Chemotherapy (Pembro Combo) | Placebo + SOC Chemotherapy (SOC) | |
|--|---|---|----------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 251 | 0 ^[19] | 243 | |
| Units: Score on a Scale | | | | |
| least squares mean (confidence interval 95%) | -1.91 (-5.81 to 1.98) | (to) | -1.75 (-5.17 to 1.66) | |

Notes:

[19] - The pembro combo arm was compared to the SOC arm separately and not included in this analysis.

Statistical analyses

| | |
|---|--|
| Statistical analysis title | EORTC-QLQ-C30 GHS/QoL: Pembro Mono vs SOC |
| Statistical analysis description: | |
| <p>Change from baseline to Week 18 in EORTC-QLQ-C30 GHS/QoL combined score was compared between all participants of the pembro mono arm and the SOC arm. Comparison based on constrained longitudinal data analysis (cLDA) model with GHS/QoL score as response variable and treatment by visit interaction and stratification factors (geographic region, disease status, and fluoropyrimidine treatment) as covariates.</p> | |
| Comparison groups | Pembrolizumab Monotherapy (Pembro Mono) v Placebo + SOC Chemotherapy (SOC) |
| Number of subjects included in analysis | 494 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.948 ^[20] |
| Method | cLDA |
| Parameter estimate | Difference in LS Means |
| Point estimate | -0.16 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.01 |
| upper limit | 4.69 |

Notes:

[20] - No formal hypothesis testing performed; nominal p-value provided for treatment comparison.

Secondary: Pembro Combo vs SOC: Change from Baseline to Week 18 in the EORTC QLQ-C30 Global Health Status/Quality of Life (Items 29 and 30) Combined Score

| | |
|-----------------|---|
| End point title | Pembro Combo vs SOC: Change from Baseline to Week 18 in the EORTC QLQ-C30 Global Health Status/Quality of Life (Items 29 and 30) Combined Score |
|-----------------|---|

End point description:

The EORTC-QLQ-C30 is a 30-item questionnaire developed to assess the quality of life of cancer patients. Participant responses to the GHS question "How would you rate your overall health during the past week?" (Item 29) and the QoL question "How would you rate your overall quality of life during the past week?" (Item 30) were scored on a 7-point scale (1=Very Poor to 7=Excellent). Using linear transformation, raw scores were standardized so that scores ranged from 0 to 100, with a higher score indicating a better overall outcome. Participants in the pembro combo arm and SOC arm who received ≥ 1 dose of study drug and who had EORTC-QLQ-C30 assessments available at baseline or post-baseline up to Week 18 were analyzed. Per protocol, change from baseline to Week 18 in the GHS/QoL combined score was compared separately between all participants of the pembro mono arm and SOC arm and is presented earlier in the record.

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

End point timeframe:

Baseline, Week 18

| End point values | Pembrolizumab Monotherapy (Pembro Mono) | Pembrolizumab + SOC Chemotherapy (Pembro Combo) | Placebo + SOC Chemotherapy (SOC) | |
|--|---|---|----------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0 ^[21] | 245 | 243 | |
| Units: Score on a Scale | | | | |
| least squares mean (confidence interval 95%) | (to) | -0.09 (-3.36 to 3.19) | -2.07 (-5.43 to 1.29) | |

Notes:

[21] - The pembro mono arm was compared to the SOC arm separately and not included in this analysis.

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | EORTC-QLQ-C30 GHS/QoL: Pembro Combo vs SOC |
|----------------------------|--|

Statistical analysis description:

Change from baseline to Week 18 in EORTC-QLQ-C30 GHS/QoL combined score was compared between all participants of the pembro combo arm and the SOC arm. Comparison based on cLDA model with GHS/QoL score as response variable and treatment by visit interaction and stratification factors (geographic region, disease status, and fluoropyrimidine treatment) as covariates.

| | |
|-------------------|--|
| Comparison groups | Pembrolizumab + SOC Chemotherapy (Pembro Combo) v Placebo + SOC Chemotherapy (SOC) |
|-------------------|--|

| | |
|---|-------------------------|
| Number of subjects included in analysis | 488 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.368 ^[22] |
| Method | cLDA |
| Parameter estimate | Difference in LS Means |
| Point estimate | 1.98 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.34 |
| upper limit | 6.31 |

Notes:

[22] - No formal hypothesis testing performed; nominal p-value provided for treatment comparison.

Secondary: Pembro Mono vs. SOC: Change from Baseline to Week 18 in EORTC QLQ-Module for Gastric Cancer (STO22) Pain Symptom Subscale Score

| | |
|-----------------|---|
| End point title | Pembro Mono vs. SOC: Change from Baseline to Week 18 in EORTC QLQ-Module for Gastric Cancer (STO22) Pain Symptom Subscale Score |
|-----------------|---|

End point description:

EORTC-QLQ-STO22 is a 22-item questionnaire developed to assess QoL of gastric cancer participants. It consists of 5 multi-item subscales that assess dysphagia (3 items), dietary restriction (4 items), pain (4 items), upper gastro-esophageal symptoms (3 items), and emotional problems (3 items), and questions on dry mouth, taste, body image, and hair loss. Participant responses to the Pain symptom subscale (Items 34-37) were scored on a 4-point scale (1=Not at all to 4=Very much). Raw scores were standardized by linear transformation so that scores ranged from 0 to 100, with a higher score indicating more problems. Participants in the pembro mono arm and SOC arm who received ≥1 dose of study drug and who had EORTC-QLQ-STO22 assessments available at baseline or post-baseline up to Week 18 were analyzed. Per protocol, change from baseline to Week 18 in the EORTC-QLQ-STO22 Pain score was compared separately between the pembro combo arm and SOC arm and is presented later in the record.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 18 | |

| End point values | Pembrolizumab Monotherapy (Pembro Mono) | Pembrolizumab + SOC Chemotherapy (Pembro Combo) | Placebo + SOC Chemotherapy (SOC) | |
|--|---|---|----------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 251 | 0 ^[23] | 243 | |
| Units: Score on a Scale | | | | |
| least squares mean (confidence interval 95%) | -1.14 (-4.67 to 2.39) | (to) | -3.49 (-6.60 to -0.38) | |

Notes:

[23] - The pembro combo arm was compared to the SOC arm separately and not included in this analysis.

Statistical analyses

| | |
|----------------------------|-------------------------------------|
| Statistical analysis title | EORTC-QLQ-STO22: Pembro Mono vs SOC |
|----------------------------|-------------------------------------|

Statistical analysis description:

Change from baseline to Week 18 in EORTC-QLQ-STO22 Pain symptom subscale score was compared between all participants of the pembro mono arm and the SOC arm. Comparison based on cLDA model with GHS/QoL score as response variable and treatment by visit interaction and stratification factors (geographic region, disease status, and fluoropyrimidine treatment) as covariates.

| | |
|---|--|
| Comparison groups | Pembrolizumab Monotherapy (Pembro Mono) v Placebo + SOC Chemotherapy (SOC) |
| Number of subjects included in analysis | 494 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.308 ^[24] |
| Method | cLDA |
| Parameter estimate | Difference in LS Means |
| Point estimate | 2.35 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.18 |
| upper limit | 6.89 |

Notes:

[24] - No formal hypothesis testing performed; nominal p-value provided for treatment comparison.

Secondary: Pembro Combo vs. SOC: Change from Baseline to Week 18 in EORTC QLQ-STO22 Pain Symptom Subscale Score

| | |
|-----------------|--|
| End point title | Pembro Combo vs. SOC: Change from Baseline to Week 18 in EORTC QLQ-STO22 Pain Symptom Subscale Score |
|-----------------|--|

End point description:

EORTC-QLQ-STO22 is a 22-item questionnaire developed to assess QoL of gastric cancer participants. It consists of 5 multi-item subscales that assess dysphagia (3 items), dietary restriction (4 items), pain (4 items), upper gastro-esophageal symptoms (3 items), and emotional problems (3 items), and questions on dry mouth, taste, body image, and hair loss. Participant responses to the Pain symptom subscale (Items 34-37) were scored on a 4-point scale (1=Not at all to 4=Very much). Raw scores were standardized by linear transformation so that scores ranged from 0 to 100, with a higher score indicating more problems. Participants in the pembro combo arm and SOC arm who received ≥1 dose of study drug and who had EORTC-QLQ-STO22 assessments available at baseline or post-baseline up to Week 18 were analyzed. Per protocol, change from baseline to Week 18 in the EORTC-QLQ-STO22 Pain score was compared separately between the pembro mono arm and SOC arm and is presented earlier in the record.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 18 | |

| End point values | Pembrolizumab Monotherapy (Pembro Mono) | Pembrolizumab + SOC Chemotherapy (Pembro Combo) | Placebo + SOC Chemotherapy (SOC) | |
|--|---|---|----------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0 ^[25] | 245 | 243 | |
| Units: Score on a Scale | | | | |
| least squares mean (confidence interval 95%) | (to) | -10.12 (-13.08 to -7.17) | -3.56 (-6.61 to -0.51) | |

Notes:

[25] - The pembro mono arm was compared to the SOC arm separately and not included in this analysis.

Statistical analyses

| | |
|---|--|
| Statistical analysis title | EORTC-QLQ-STO22: Pembro Combo vs SOC |
| Statistical analysis description: | |
| Change from baseline to Week 18 in EORTC-QLQ-STO22 Pain symptom subscale score was compared between all participants of the pembro combo arm and the SOC arm. Comparison based on cLDA model with GHS/QoL score as response variable and treatment by visit interaction and stratification factors (geographic region, disease status, and fluoropyrimidine treatment) as covariates. | |
| Comparison groups | Pembrolizumab + SOC Chemotherapy (Pembro Combo) v Placebo + SOC Chemotherapy (SOC) |
| Number of subjects included in analysis | 488 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.001 ^[26] |
| Method | cLDA |
| Parameter estimate | Difference in LS Means |
| Point estimate | -6.56 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10.55 |
| upper limit | -2.58 |

Notes:

[26] - No formal hypothesis testing performed; nominal p-value provided for treatment comparison.

Secondary: Number of Participants Experiencing an Adverse Event (AE)

| | |
|--|---|
| End point title | Number of Participants Experiencing an Adverse Event (AE) |
| End point description: | |
| An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which did not necessarily have a causal relationship with this treatment. An AE could therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening of a pre-existing condition that was temporally associated with the use of the Sponsor's product was also an adverse event. The number of participants who experienced an AE was reported for each arm according to the treatment received. All randomized participants who received at least 1 dose of trial treatment were analyzed. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to approximately 33 months | |

| End point values | Pembrolizumab Monotherapy (Pembro Mono) | Pembrolizumab + SOC Chemotherapy (Pembro Combo) | Placebo + SOC Chemotherapy (SOC) | |
|-----------------------------|---|---|----------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 254 | 250 | 244 | |
| Units: Participants | 242 | 244 | 240 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Discontinuing Study Treatment Due to an AE

| | |
|-----------------|---|
| End point title | Number of Participants Discontinuing Study Treatment Due to an AE |
|-----------------|---|

End point description:

An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which did not necessarily have a causal relationship with this treatment. An AE could therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening of a pre-existing condition that was temporally associated with the use of the Sponsor's product was also an adverse event. The number of participants who discontinued study treatment due to an AE was reported for each arm according to the treatment received. All randomized participants who received at least 1 dose of trial treatment were analyzed.

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

End point timeframe:

Up to approximately 30 months

| End point values | Pembrolizumab Monotherapy (Pembro Mono) | Pembrolizumab + SOC Chemotherapy (Pembro Combo) | Placebo + SOC Chemotherapy (SOC) | |
|-----------------------------|---|---|----------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 254 | 250 | 244 | |
| Units: Participants | 29 | 85 | 58 | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 78 months

Adverse event reporting additional description:

All-Cause Mortality reported for all randomized participants. Serious AEs and Other AEs were reported for all randomized participants who received at least 1 dose of study treatment. Per protocol, MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to study drug are excluded as AEs.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 25.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Pembrolizumab Monotherapy (Pembro Mono) First Course |
|-----------------------|--|

Reporting group description:

Participants received pembrolizumab 200 mg IV Q3W.

| | |
|-----------------------|--|
| Reporting group title | Pembrolizumab + SOC Chemotherapy (Pembro Combo)-First Course |
|-----------------------|--|

Reporting group description:

Participants received pembrolizumab 200 mg Q3W plus cisplatin 80 mg/m² Q3W plus 5-FU 800 mg/m²/day IV infusion on Days 1-5 Q3W. Capecitabine 1000 mg/m² twice a day (BID) on Days 1-14 Q3W could be substituted for 5-FU per local guidelines.

| | |
|-----------------------|--|
| Reporting group title | Pembrolizumab + SOC Chemotherapy-Second Course |
|-----------------------|--|

Reporting group description:

Eligible participants who stopped the initial course of pembrolizumab (200 mg IV Q3W for up to 35 treatments [approximately 2 years]) administered in combination with SOC chemotherapy, and experienced Stable Disease (SD) or better but progressed after discontinuation initiated a second course of pembrolizumab at the investigator's discretion for up to 17 cycles (up to approximately 1 additional year).

| | |
|-----------------------|---|
| Reporting group title | Pembrolizumab Monotherapy Second Course |
|-----------------------|---|

Reporting group description:

Eligible participants who stopped the initial course of pembrolizumab (200 mg IV Q3W for up to 35 treatments [approximately 2 years]) with Stable Disease (SD) or better but progressed after discontinuation initiated a second course of pembrolizumab at the investigator's discretion for up to 17 cycles (up to approximately 1 additional year).

| | |
|-----------------------|---|
| Reporting group title | Placebo + SOC Chemotherapy (SOC)-First Course |
|-----------------------|---|

Reporting group description:

Participants received placebo IV Q3W plus cisplatin 80 mg/m² Q3W plus 5-FU 800 mg/m²/day IV infusion on Days 1-5 Q3W. Capecitabine 1000 mg/m² BID on Days 1-14 Q3W could be substituted for 5-FU per local guidelines.

| Serious adverse events | Pembrolizumab Monotherapy (Pembro Mono) First Course | Pembrolizumab + SOC Chemotherapy (Pembro Combo)-First Course | Pembrolizumab + SOC Chemotherapy-Second Course |
|---|--|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 93 / 254 (36.61%) | 122 / 250 (48.80%) | 0 / 5 (0.00%) |
| number of deaths (all causes) | 229 | 232 | 1 |
| number of deaths resulting from adverse events | 3 | 5 | 0 |

| | | | |
|---|-----------------|-----------------|---------------|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Uterine cancer | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oncologic complication | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal cancer | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour haemorrhage | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 2 / 250 (0.80%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour pain | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 2 / 250 (0.80%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Embolism | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|--|-----------------|-----------------|---------------|
| Hypertension | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotension | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Superficial vein thrombosis | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 3 / 250 (1.20%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|---------------|
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 2 / 254 (0.79%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 2 / 250 (0.80%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malaise | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 3 / 250 (1.20%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Death | | | |
| subjects affected / exposed | 6 / 254 (2.36%) | 3 / 250 (1.20%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 6 | 0 / 3 | 0 / 0 |
| Pain | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |

| | | | |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed | 2 / 254 (0.79%) | 5 / 250 (2.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral swelling | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 2 / 254 (0.79%) | 8 / 250 (3.20%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 6 / 9 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 3 / 254 (1.18%) | 2 / 250 (0.80%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |

| | | | |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory arrest | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 2 / 254 (0.79%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Completed suicide | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Depression | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Product issues | | | |
| Device dislocation | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |

| | | | |
|---|-----------------|-----------------|---------------|
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood calcium decreased | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood magnesium decreased | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Creatinine renal clearance decreased | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |

| | | | |
|---|-----------------|-----------------|---------------|
| Lower limb fracture | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anastomotic stenosis | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Procedural pain | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subdural haematoma | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subdural haemorrhage | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Toxicity to various agents | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |

| | | | |
|---|-----------------|-----------------|---------------|
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arrhythmia | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericardial effusion | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Extrasystoles | | | |

| | | | |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral infarction | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral thrombosis | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral venous sinus thrombosis | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalopathy | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Dizziness | | | |

| | | | |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dizziness postural | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Embolic stroke | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Presyncope | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |

| | | | |
|---|-----------------|------------------|---------------|
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 2 / 250 (0.80%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 9 / 250 (3.60%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 8 / 9 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Anaemia | | | |
| subjects affected / exposed | 3 / 254 (1.18%) | 12 / 250 (4.80%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 11 / 14 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 3 / 250 (1.20%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypochromic anaemia | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 2 / 250 (0.80%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancytopenia | | | |

| | | | |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo positional | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Colitis | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 6 / 250 (2.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 6 / 6 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ascites | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 4 / 250 (1.60%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 3 / 250 (1.20%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroesophageal reflux disease | | | |

| | | | |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal obstruction | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 2 / 254 (0.79%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Gastric perforation | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 5 / 254 (1.97%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 1 / 6 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Enterocolitis | | | |
| subjects affected / exposed | 2 / 254 (0.79%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Dysphagia | | | |
| subjects affected / exposed | 2 / 254 (0.79%) | 3 / 250 (1.20%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 7 / 250 (2.80%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 6 / 7 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ileus | | | |

| | | | |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed | 3 / 254 (1.18%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 2 / 250 (0.80%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 5 / 250 (2.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 7 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Melaena | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophageal obstruction | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 2 / 250 (0.80%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Obstruction gastric | | | |
| subjects affected / exposed | 2 / 254 (0.79%) | 2 / 250 (0.80%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Incarcerated hiatus hernia | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |

| | | | |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal perforation | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestine perforation | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mechanical ileus | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 3 / 254 (1.18%) | 6 / 250 (2.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 3 / 7 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 3 / 254 (1.18%) | 2 / 250 (0.80%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 2 / 250 (0.80%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal obstruction | | | |

| | | | |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Salivary hypersecretion | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritoneocutaneous fistula | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subileus | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Biliary obstruction | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 2 / 250 (0.80%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Autoimmune hepatitis | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholangitis acute | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis | | | |

| | | | |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic cirrhosis | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Hepatitis | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholangitis | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Jaundice cholestatic | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Jaundice | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune-mediated hepatitis | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertransaminasaemia | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Liver disorder | | | |

| | | | |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Diabetic foot | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stevens-Johnson syndrome | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 4 / 254 (1.57%) | 8 / 250 (3.20%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 5 / 8 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Autoimmune nephritis | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydronephrosis | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tubulointerstitial nephritis | | | |
| subjects affected / exposed | 2 / 254 (0.79%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prerenal failure | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |

| | | | |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed | 1 / 254 (0.39%) | 3 / 250 (1.20%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal impairment | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal injury | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephritis | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract obstruction | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Addison's disease | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypothyroidism | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypophysitis | | | |

| | | | |
|--|-----------------|-----------------|---------------|
| subjects affected / exposed | 1 / 254 (0.39%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Compartment syndrome | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myalgia | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myositis | | | |
| subjects affected / exposed | 2 / 254 (0.79%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Bacteraemia | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|---------------|
| Appendicitis perforated | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Amoebiasis | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal sepsis | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Biliary tract infection | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Candida sepsis | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |

| | | | |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enterocolitis infectious | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocarditis | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Device related infection | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal infection | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 2 / 254 (0.79%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection bacterial | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Meningitis | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meningitis tuberculous | | | |

| | | | |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Oesophageal candidiasis | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pharyngitis bacterial | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 5 / 254 (1.97%) | 7 / 250 (2.80%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 3 / 7 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia klebsiella | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostate infection | | | |

| | | | |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Staphylococcal bacteraemia | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary tuberculosis | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary sepsis | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |

| | | | |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed | 0 / 254 (0.00%) | 2 / 250 (0.80%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular device infection | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 2 / 250 (0.80%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound infection | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Cachexia | | | |
| subjects affected / exposed | 2 / 254 (0.79%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Decreased appetite | | | |
| subjects affected / exposed | 3 / 254 (1.18%) | 2 / 250 (0.80%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 2 / 250 (0.80%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetic ketoacidosis | | | |

| | | | |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dehydration | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 7 / 250 (2.80%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 6 / 8 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 2 / 250 (0.80%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 3 / 250 (1.20%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 5 / 254 (1.97%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 2 / 5 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Refeeding syndrome | | | |

| | | | |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed | 0 / 254 (0.00%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Type 1 diabetes mellitus | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 1 / 250 (0.40%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malnutrition | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 0 / 250 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Pembrolizumab Monotherapy Second Course | Placebo + SOC Chemotherapy (SOC)-First Course | |
|---|---|---|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 117 / 244 (47.95%) | |
| number of deaths (all causes) | 2 | 240 | |
| number of deaths resulting from adverse events | 0 | 3 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Uterine cancer | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oncologic complication | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal cancer | | | |

| | | | |
|---|---------------|-----------------|--|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour haemorrhage | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 3 / 244 (1.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Embolism | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Orthostatic hypotension | | | |

| | | | |
|--|---------------|-----------------|--|
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Superficial vein thrombosis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 2 / 244 (0.82%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Mucosal inflammation | | | |

| | | | |
|---|---------------|-----------------|--|
| subjects affected / exposed | 0 / 4 (0.00%) | 3 / 244 (1.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malaise | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 5 / 244 (2.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral swelling | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |

| | | | |
|---|---------------|------------------|--|
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 13 / 244 (5.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 9 / 13 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory arrest | | | |

| | | | |
|---|---------------|-----------------|--|
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Completed suicide | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 2 / 244 (0.82%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Depression | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Product issues | | | |
| Device dislocation | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---------------|-----------------|--|
| Blood calcium decreased subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood creatinine increased subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood magnesium decreased subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Creatinine renal clearance decreased subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic enzyme increased subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transaminases increased subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Lower limb fracture subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip fracture subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---------------|-----------------|--|
| Anastomotic stenosis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Procedural pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural haematoma | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural haemorrhage | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Toxicity to various agents | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arrhythmia | | | |

| | | | |
|---|---------------|-----------------|--|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Extrasystoles | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure | | | |

| | | | |
|---|---------------|-----------------|--|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral infarction | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral thrombosis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral venous sinus thrombosis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Encephalopathy | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness postural | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Embolic stroke | | | |

| | | | |
|---|---------------|-----------------|--|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Presyncope | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 3 / 244 (1.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |

| | | | |
|---|---------------|------------------|--|
| subjects affected / exposed | 0 / 4 (0.00%) | 7 / 244 (2.87%) | |
| occurrences causally related to treatment / all | 0 / 0 | 7 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 10 / 244 (4.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 12 / 13 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypochromic anaemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 3 / 244 (1.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Vertigo positional | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |

| | | | |
|---|---------------|-----------------|--|
| Colitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ascites | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 2 / 244 (0.82%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 2 / 244 (0.82%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal obstruction | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |

| | | | |
|---|---------------|-----------------|--|
| subjects affected / exposed | 0 / 4 (0.00%) | 3 / 244 (1.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric perforation | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterocolitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 5 / 244 (2.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 9 / 244 (3.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 9 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |

| | | | |
|---|---------------|-----------------|--|
| subjects affected / exposed | 0 / 4 (0.00%) | 5 / 244 (2.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Melaena | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal obstruction | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Obstruction gastric | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 3 / 244 (1.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Incarcerated hiatus hernia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Intestinal perforation | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestine perforation | | | |

| | | | |
|---|---------------|------------------|--|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mechanical ileus | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 12 / 244 (4.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 11 / 15 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 2 / 244 (0.82%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 3 / 244 (1.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 2 / 244 (0.82%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Salivary hypersecretion | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritoneocutaneous fistula | | | |

| | | | |
|---|---------------|-----------------|--|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subileus | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Biliary obstruction | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Autoimmune hepatitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholangitis acute | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic cirrhosis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis | | | |

| | | | |
|---|---------------|-----------------|--|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholangitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jaundice cholestatic | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jaundice | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune-mediated hepatitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertransaminasaemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver disorder | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Diabetic foot | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stevens-Johnson syndrome | | | |

| | | | |
|---|---------------|-----------------|--|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 8 / 244 (3.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 5 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Autoimmune nephritis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydronephrosis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tubulointerstitial nephritis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prerenal failure | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 2 / 244 (0.82%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal impairment | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal injury | | | |

| | | | |
|---|---------------|-----------------|--|
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephritis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract obstruction | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Addison's disease | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypothyroidism | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypophysitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 2 / 244 (0.82%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---------------|-----------------|--|
| Arthralgia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Compartment syndrome | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myalgia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myositis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Bacteraemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis perforated | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Amoebiasis | | | |

| | | | |
|---|---------------|-----------------|--|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal sepsis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Biliary tract infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Candida sepsis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterocolitis infectious | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocarditis | | | |

| | | | |
|---|---------------|-----------------|--|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection bacterial | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningitis tuberculous | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal candidiasis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oral candidiasis | | | |

| | | | |
|---|---------------|-----------------|--|
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pharyngitis bacterial | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 8 / 244 (3.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 3 | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia klebsiella | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostate infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal bacteraemia | | | |

| | | | |
|---|---------------|-----------------|--|
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 3 / 244 (1.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 4 / 244 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary tuberculosis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary sepsis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular device infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |

| | | | |
|---|----------------|-----------------|--|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 5 / 244 (2.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Cachexia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 5 / 244 (2.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 5 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperkalaemia | | | |

| | | | |
|---|---------------|-----------------|--|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 7 / 244 (2.87%) | |
| occurrences causally related to treatment / all | 0 / 0 | 6 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 3 / 244 (1.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 2 / 244 (0.82%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 2 / 244 (0.82%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Refeeding syndrome | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Type 1 diabetes mellitus | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Type 2 diabetes mellitus | | | |

| | | | |
|---|---------------|-----------------|--|
| subjects affected / exposed | 0 / 4 (0.00%) | 2 / 244 (0.82%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malnutrition | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 244 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Pembrolizumab Monotherapy (Pembro Mono) First Course | Pembrolizumab + SOC Chemotherapy (Pembro Combo)- First Course | Pembrolizumab + SOC Chemotherapy- Second Course |
|---|--|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 216 / 254 (85.04%) | 239 / 250 (95.60%) | 5 / 5 (100.00%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 11 / 254 (4.33%) | 10 / 250 (4.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 12 | 13 | 1 |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 4 / 254 (1.57%) | 14 / 250 (5.60%) | 0 / 5 (0.00%) |
| occurrences (all) | 6 | 16 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 49 / 254 (19.29%) | 105 / 250 (42.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 63 | 156 | 0 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 3 / 254 (1.18%) | 41 / 250 (16.40%) | 0 / 5 (0.00%) |
| occurrences (all) | 5 | 57 | 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 13 / 254 (5.12%) | 16 / 250 (6.40%) | 0 / 5 (0.00%) |
| occurrences (all) | 14 | 16 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 25 / 254 (9.84%) | 32 / 250 (12.80%) | 0 / 5 (0.00%) |
| occurrences (all) | 33 | 38 | 0 |
| Asthenia | | | |

| | | | |
|--|-------------------------|-------------------------|--------------------|
| subjects affected / exposed occurrences (all) | 30 / 254 (11.81%) 33 | 41 / 250 (16.40%) 53 | 0 / 5 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Hiccups | | | |
| subjects affected / exposed | 1 / 254 (0.39%) | 16 / 250 (6.40%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 20 | 0 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 5 / 250 (2.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 5 | 1 |
| Dyspnoea | | | |
| subjects affected / exposed | 11 / 254 (4.33%) | 19 / 250 (7.60%) | 0 / 5 (0.00%) |
| occurrences (all) | 16 | 23 | 0 |
| Dysphonia | | | |
| subjects affected / exposed | 3 / 254 (1.18%) | 1 / 250 (0.40%) | 1 / 5 (20.00%) |
| occurrences (all) | 3 | 1 | 1 |
| Cough | | | |
| subjects affected / exposed | 19 / 254 (7.48%) | 24 / 250 (9.60%) | 0 / 5 (0.00%) |
| occurrences (all) | 23 | 26 | 0 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 21 / 254 (8.27%) | 18 / 250 (7.20%) | 1 / 5 (20.00%) |
| occurrences (all) | 21 | 19 | 1 |
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 8 / 254 (3.15%) | 30 / 250 (12.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 8 | 52 | 0 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 13 / 254 (5.12%) | 7 / 250 (2.80%) | 0 / 5 (0.00%) |
| occurrences (all) | 16 | 8 | 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 18 / 254 (7.09%) | 9 / 250 (3.60%) | 0 / 5 (0.00%) |
| occurrences (all) | 22 | 10 | 0 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 4 / 254 (1.57%) | 30 / 250 (12.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 6 | 71 | 0 |
| Weight decreased | | | |

| | | | |
|---|-------------------------|---------------------------|--------------------|
| subjects affected / exposed occurrences (all) | 28 / 254 (11.02%) 28 | 54 / 250 (21.60%) 63 | 0 / 5 (0.00%) 0 |
| Platelet count decreased subjects affected / exposed occurrences (all) | 3 / 254 (1.18%) 3 | 23 / 250 (9.20%) 38 | 0 / 5 (0.00%) 0 |
| Neutrophil count decreased subjects affected / exposed occurrences (all) | 4 / 254 (1.57%) 15 | 59 / 250 (23.60%) 120 | 0 / 5 (0.00%) 0 |
| Blood uric acid increased subjects affected / exposed occurrences (all) | 2 / 254 (0.79%) 2 | 0 / 250 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Nervous system disorders | | | |
| Dizziness subjects affected / exposed occurrences (all) | 14 / 254 (5.51%) 18 | 20 / 250 (8.00%) 21 | 0 / 5 (0.00%) 0 |
| Headache subjects affected / exposed occurrences (all) | 16 / 254 (6.30%) 18 | 24 / 250 (9.60%) 26 | 0 / 5 (0.00%) 0 |
| Neuropathy peripheral subjects affected / exposed occurrences (all) | 0 / 254 (0.00%) 0 | 31 / 250 (12.40%) 36 | 0 / 5 (0.00%) 0 |
| Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 3 / 254 (1.18%) 3 | 34 / 250 (13.60%) 37 | 0 / 5 (0.00%) 0 |
| Dysgeusia subjects affected / exposed occurrences (all) | 4 / 254 (1.57%) 4 | 16 / 250 (6.40%) 18 | 0 / 5 (0.00%) 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 61 / 254 (24.02%) 73 | 112 / 250 (44.80%) 150 | 0 / 5 (0.00%) 0 |
| Leukopenia subjects affected / exposed occurrences (all) | 0 / 254 (0.00%) 0 | 21 / 250 (8.40%) 52 | 0 / 5 (0.00%) 0 |
| Neutropenia | | | |

| | | | |
|-----------------------------|-------------------|-------------------|----------------|
| subjects affected / exposed | 1 / 254 (0.39%) | 95 / 250 (38.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 2 | 201 | 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 2 / 254 (0.79%) | 27 / 250 (10.80%) | 0 / 5 (0.00%) |
| occurrences (all) | 5 | 38 | 0 |
| Ear and labyrinth disorders | | | |
| Tinnitus | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 22 / 250 (8.80%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 24 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 13 / 254 (5.12%) | 9 / 250 (3.60%) | 0 / 5 (0.00%) |
| occurrences (all) | 21 | 11 | 0 |
| Abdominal discomfort | | | |
| subjects affected / exposed | 2 / 254 (0.79%) | 6 / 250 (2.40%) | 0 / 5 (0.00%) |
| occurrences (all) | 2 | 7 | 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 46 / 254 (18.11%) | 41 / 250 (16.40%) | 1 / 5 (20.00%) |
| occurrences (all) | 56 | 49 | 1 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 23 / 254 (9.06%) | 24 / 250 (9.60%) | 0 / 5 (0.00%) |
| occurrences (all) | 26 | 27 | 0 |
| Ascites | | | |
| subjects affected / exposed | 6 / 254 (2.36%) | 8 / 250 (3.20%) | 0 / 5 (0.00%) |
| occurrences (all) | 7 | 8 | 0 |
| Constipation | | | |
| subjects affected / exposed | 36 / 254 (14.17%) | 71 / 250 (28.40%) | 0 / 5 (0.00%) |
| occurrences (all) | 43 | 108 | 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 35 / 254 (13.78%) | 83 / 250 (33.20%) | 0 / 5 (0.00%) |
| occurrences (all) | 60 | 153 | 0 |
| Dyspepsia | | | |
| subjects affected / exposed | 16 / 254 (6.30%) | 13 / 250 (5.20%) | 0 / 5 (0.00%) |
| occurrences (all) | 18 | 18 | 0 |
| Dysphagia | | | |

| | | | |
|---|-------------------|--------------------|----------------|
| subjects affected / exposed | 11 / 254 (4.33%) | 15 / 250 (6.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 11 | 17 | 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 8 / 254 (3.15%) | 6 / 250 (2.40%) | 0 / 5 (0.00%) |
| occurrences (all) | 8 | 7 | 0 |
| Nausea | | | |
| subjects affected / exposed | 49 / 254 (19.29%) | 162 / 250 (64.80%) | 0 / 5 (0.00%) |
| occurrences (all) | 59 | 295 | 0 |
| Stomatitis | | | |
| subjects affected / exposed | 5 / 254 (1.97%) | 33 / 250 (13.20%) | 0 / 5 (0.00%) |
| occurrences (all) | 6 | 49 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 49 / 254 (19.29%) | 84 / 250 (33.60%) | 0 / 5 (0.00%) |
| occurrences (all) | 64 | 148 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 20 / 254 (7.87%) | 31 / 250 (12.40%) | 1 / 5 (20.00%) |
| occurrences (all) | 23 | 41 | 1 |
| Pruritus | | | |
| subjects affected / exposed | 22 / 254 (8.66%) | 21 / 250 (8.40%) | 1 / 5 (20.00%) |
| occurrences (all) | 27 | 25 | 1 |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 60 / 250 (24.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 69 | 0 |
| Dry skin | | | |
| subjects affected / exposed | 6 / 254 (2.36%) | 15 / 250 (6.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 6 | 16 | 0 |
| Alopecia | | | |
| subjects affected / exposed | 2 / 254 (0.79%) | 19 / 250 (7.60%) | 0 / 5 (0.00%) |
| occurrences (all) | 2 | 19 | 0 |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 0 / 254 (0.00%) | 3 / 250 (1.20%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Endocrine disorders | | | |

| | | | |
|---|-------------------------|-------------------------|--------------------|
| Hypothyroidism subjects affected / exposed occurrences (all) | 21 / 254 (8.27%) 21 | 28 / 250 (11.20%) 29 | 0 / 5 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 19 / 254 (7.48%) 20 | 22 / 250 (8.80%) 25 | 0 / 5 (0.00%) 0 |
| Back pain subjects affected / exposed occurrences (all) | 30 / 254 (11.81%) 32 | 13 / 250 (5.20%) 14 | 0 / 5 (0.00%) 0 |
| Pain in extremity subjects affected / exposed occurrences (all) | 4 / 254 (1.57%) 4 | 17 / 250 (6.80%) 23 | 0 / 5 (0.00%) 0 |
| Infections and infestations | | | |
| Pneumonia subjects affected / exposed occurrences (all) | 8 / 254 (3.15%) 8 | 13 / 250 (5.20%) 13 | 0 / 5 (0.00%) 0 |
| Metabolism and nutrition disorders | | | |
| Hypomagnesaemia subjects affected / exposed occurrences (all) | 3 / 254 (1.18%) 11 | 34 / 250 (13.60%) 43 | 0 / 5 (0.00%) 0 |
| Hyponatraemia subjects affected / exposed occurrences (all) | 15 / 254 (5.91%) 16 | 12 / 250 (4.80%) 21 | 0 / 5 (0.00%) 0 |
| Hypophosphataemia subjects affected / exposed occurrences (all) | 2 / 254 (0.79%) 2 | 15 / 250 (6.00%) 21 | 0 / 5 (0.00%) 0 |
| Hypokalaemia subjects affected / exposed occurrences (all) | 11 / 254 (4.33%) 16 | 35 / 250 (14.00%) 49 | 0 / 5 (0.00%) 0 |
| Hypocalcaemia subjects affected / exposed occurrences (all) | 9 / 254 (3.54%) 10 | 14 / 250 (5.60%) 20 | 0 / 5 (0.00%) 0 |
| Hypoalbuminaemia subjects affected / exposed occurrences (all) | 18 / 254 (7.09%) 21 | 17 / 250 (6.80%) 21 | 0 / 5 (0.00%) 0 |

| | | | |
|-----------------------------|-------------------|-------------------|---------------|
| Dehydration | | | |
| subjects affected / exposed | 7 / 254 (2.76%) | 11 / 250 (4.40%) | 0 / 5 (0.00%) |
| occurrences (all) | 7 | 14 | 0 |
| Decreased appetite | | | |
| subjects affected / exposed | 48 / 254 (18.90%) | 94 / 250 (37.60%) | 0 / 5 (0.00%) |
| occurrences (all) | 53 | 135 | 0 |

| Non-serious adverse events | Pembrolizumab Monotherapy Second Course | Placebo + SOC Chemotherapy (SOC)-First Course | |
|---|---|---|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 3 / 4 (75.00%) | 234 / 244 (95.90%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 12 / 244 (4.92%) | |
| occurrences (all) | 2 | 17 | |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 7 / 244 (2.87%) | |
| occurrences (all) | 0 | 7 | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 75 / 244 (30.74%) | |
| occurrences (all) | 0 | 112 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 34 / 244 (13.93%) | |
| occurrences (all) | 0 | 62 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 19 / 244 (7.79%) | |
| occurrences (all) | 0 | 22 | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 25 / 244 (10.25%) | |
| occurrences (all) | 0 | 26 | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 47 / 244 (19.26%) | |
| occurrences (all) | 0 | 81 | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|--------------------------------------|---------------|-------------------|--|
| Hiccups | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 12 / 244 (4.92%) | |
| occurrences (all) | 0 | 21 | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 10 / 244 (4.10%) | |
| occurrences (all) | 0 | 12 | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 9 / 244 (3.69%) | |
| occurrences (all) | 0 | 11 | |
| Dysphonia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 2 / 244 (0.82%) | |
| occurrences (all) | 0 | 2 | |
| Cough | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 23 / 244 (9.43%) | |
| occurrences (all) | 0 | 26 | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 22 / 244 (9.02%) | |
| occurrences (all) | 0 | 24 | |
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 34 / 244 (13.93%) | |
| occurrences (all) | 0 | 59 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 9 / 244 (3.69%) | |
| occurrences (all) | 0 | 9 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 11 / 244 (4.51%) | |
| occurrences (all) | 0 | 12 | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 25 / 244 (10.25%) | |
| occurrences (all) | 0 | 52 | |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 33 / 244 (13.52%) | |
| occurrences (all) | 0 | 33 | |
| Platelet count decreased | | | |

| | | | |
|--------------------------------------|----------------|--------------------|--|
| subjects affected / exposed | 0 / 4 (0.00%) | 17 / 244 (6.97%) | |
| occurrences (all) | 0 | 21 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 40 / 244 (16.39%) | |
| occurrences (all) | 0 | 79 | |
| Blood uric acid increased | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 1 / 244 (0.41%) | |
| occurrences (all) | 1 | 1 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 15 / 244 (6.15%) | |
| occurrences (all) | 0 | 22 | |
| Headache | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 16 / 244 (6.56%) | |
| occurrences (all) | 0 | 22 | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 16 / 244 (6.56%) | |
| occurrences (all) | 0 | 17 | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 16 / 244 (6.56%) | |
| occurrences (all) | 0 | 18 | |
| Dysgeusia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 20 / 244 (8.20%) | |
| occurrences (all) | 0 | 21 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 3 / 4 (75.00%) | 108 / 244 (44.26%) | |
| occurrences (all) | 3 | 144 | |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 26 / 244 (10.66%) | |
| occurrences (all) | 0 | 51 | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 102 / 244 (41.80%) | |
| occurrences (all) | 0 | 222 | |
| Thrombocytopenia | | | |

| | | | |
|--|---------------------|--------------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 26 / 244 (10.66%) 33 | |
| Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 20 / 244 (8.20%) 20 | |
| Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 10 / 244 (4.10%) 10 | |
| Abdominal discomfort subjects affected / exposed occurrences (all) | 1 / 4 (25.00%) 1 | 2 / 244 (0.82%) 2 | |
| Abdominal pain subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 41 / 244 (16.80%) 54 | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 23 / 244 (9.43%) 25 | |
| Ascites subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 14 / 244 (5.74%) 15 | |
| Constipation subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 68 / 244 (27.87%) 83 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 71 / 244 (29.10%) 106 | |
| Dyspepsia subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 11 / 244 (4.51%) 13 | |
| Dysphagia subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 16 / 244 (6.56%) 20 | |
| Gastrooesophageal reflux disease | | | |

| | | | |
|---|----------------|--------------------|--|
| subjects affected / exposed | 0 / 4 (0.00%) | 13 / 244 (5.33%) | |
| occurrences (all) | 0 | 14 | |
| Nausea | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 129 / 244 (52.87%) | |
| occurrences (all) | 0 | 236 | |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 35 / 244 (14.34%) | |
| occurrences (all) | 0 | 39 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 79 / 244 (32.38%) | |
| occurrences (all) | 0 | 142 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 15 / 244 (6.15%) | |
| occurrences (all) | 0 | 18 | |
| Pruritus | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 8 / 244 (3.28%) | |
| occurrences (all) | 1 | 11 | |
| Palmar-plantar erythrodysesthesia syndrome | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 46 / 244 (18.85%) | |
| occurrences (all) | 0 | 57 | |
| Dry skin | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 15 / 244 (6.15%) | |
| occurrences (all) | 0 | 15 | |
| Alopecia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 11 / 244 (4.51%) | |
| occurrences (all) | 0 | 11 | |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 2 / 244 (0.82%) | |
| occurrences (all) | 1 | 2 | |
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 10 / 244 (4.10%) | |
| occurrences (all) | 0 | 11 | |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|------------------------------------|---------------|-------------------|--|
| Arthralgia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 7 / 244 (2.87%) | |
| occurrences (all) | 0 | 7 | |
| Back pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 14 / 244 (5.74%) | |
| occurrences (all) | 0 | 15 | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 8 / 244 (3.28%) | |
| occurrences (all) | 0 | 9 | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 2 / 244 (0.82%) | |
| occurrences (all) | 0 | 2 | |
| Metabolism and nutrition disorders | | | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 32 / 244 (13.11%) | |
| occurrences (all) | 0 | 48 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 20 / 244 (8.20%) | |
| occurrences (all) | 0 | 26 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 9 / 244 (3.69%) | |
| occurrences (all) | 0 | 16 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 42 / 244 (17.21%) | |
| occurrences (all) | 0 | 61 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 14 / 244 (5.74%) | |
| occurrences (all) | 0 | 16 | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 23 / 244 (9.43%) | |
| occurrences (all) | 0 | 28 | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 16 / 244 (6.56%) | |
| occurrences (all) | 0 | 19 | |
| Decreased appetite | | | |

| | | | |
|-----------------------------|---------------|-------------------|--|
| subjects affected / exposed | 0 / 4 (0.00%) | 90 / 244 (36.89%) | |
| occurrences (all) | 0 | 127 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 29 July 2016 | Major changes of Amendment (AM) 3 include clarification of Inclusion and Exclusion Criteria and revision of Withdrawal/Discontinuation Criteria. |
| 06 October 2016 | Major changes of AM 5 include revision of Inclusion and Exclusion Criteria. |
| 08 March 2017 | Major changes of AM 6 include removing primary PFS hypothesis comparing pembrolizumab monotherapy to SOC, and adding primary OS hypothesis evaluating non-inferiority of pembrolizumab monotherapy. Secondary ORR hypothesis comparing pembrolizumab plus SOC vs. SOC was added. |
| 15 January 2018 | Major changes of AM 8 included revising dose modification language and adding survival status follow-up to the study. |
| 11 May 2018 | Major changes of AM 10 included the addition of 2 primary hypotheses for OS: pembrolizumab plus SOC vs. SOC, and pembrolizumab monotherapy vs. SOC in participants with CPS \geq 10. |
| 22 January 2019 | Major changes of AM 12 included revision of Prohibited Concomitant Medication language and safety follow-up language. |
| 02 August 2021 | Major changes of AM 14 included the revision of sections of the protocol including the Trial Summary and Study Diagram to include study extension language, and updating the Dose Modification and Toxicity Management Guidelines for immune response AEs per Food and Drug Administration request. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported