



Clinical trial results:

A Randomized Phase 3 Study of Nivolumab Plus Ipilimumab or Nivolumab Combined With Fluorouracil Plus Cisplatin Versus Fluorouracil Plus Cisplatin in Subjects With Unresectable Advanced, Recurrent or Metastatic Previously Untreated Esophageal Squamous Cell Carcinoma

Summary

| | |
|--------------------------|----------------------------|
| EudraCT number | 2016-001514-20 |
| Trial protocol | CZ ES GB PL FR DK PT IT RO |
| Global end of trial date | 13 January 2025 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 23 January 2026 |
| First version publication date | 23 January 2026 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | CA209-648 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03143153 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Bristol-Myers Squibb |
| Sponsor organisation address | Chaussée de la Hulpe 185, Brussels, Belgium, |
| Public contact | Global Submission Management, Clinical Trials, Bristol-Myers Squibb International Corporation, mg-gsm-ct@bms.com |
| Scientific contact | Global Submission Management, Clinical Trials, Bristol-Myers Squibb International Corporation, Clinical.Trails@bms.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 | 16 February 2025 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 18 January 2021 |
| Global end of trial reached? | Yes |
| Global end of trial date | 13 January 2025 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this study is to compare how long subjects with esophageal cancer live overall or live without disease progression after receiving nivolumab and ipilimumab or nivolumab combined with fluorouracil plus cisplatin versus fluorouracil plus cisplatin

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial participants were followed.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 29 June 2017 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 5 Years |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Argentina: 18 |
| Country: Number of subjects enrolled | Australia: 2 |
| Country: Number of subjects enrolled | Austria: 1 |
| Country: Number of subjects enrolled | Brazil: 50 |
| Country: Number of subjects enrolled | Canada: 4 |
| Country: Number of subjects enrolled | Chile: 7 |
| Country: Number of subjects enrolled | China: 112 |
| Country: Number of subjects enrolled | Colombia: 5 |
| Country: Number of subjects enrolled | Czechia: 10 |
| Country: Number of subjects enrolled | Denmark: 6 |
| Country: Number of subjects enrolled | France: 29 |
| Country: Number of subjects enrolled | Hong Kong: 9 |
| Country: Number of subjects enrolled | Italy: 15 |
| Country: Number of subjects enrolled | Japan: 395 |
| Country: Number of subjects enrolled | Korea, Republic of: 63 |
| Country: Number of subjects enrolled | Mexico: 6 |
| Country: Number of subjects enrolled | Peru: 7 |

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Poland: 21 |
| Country: Number of subjects enrolled | Romania: 26 |
| Country: Number of subjects enrolled | Russian Federation: 15 |
| Country: Number of subjects enrolled | Singapore: 7 |
| Country: Number of subjects enrolled | Spain: 4 |
| Country: Number of subjects enrolled | Taiwan: 94 |
| Country: Number of subjects enrolled | Türkiye: 6 |
| Country: Number of subjects enrolled | United Kingdom: 34 |
| Country: Number of subjects enrolled | United States: 24 |
| Worldwide total number of subjects | 970 |
| EEA total number of subjects | 112 |

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) | 518 |
| From 65 to 84 years | 449 |
| 85 years and over | 3 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

970 participants randomized, 936 treated.

Period 1

| | |
|------------------------------|-------------------------|
| Period 1 title | Pre-Treatment |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

Are arms mutually exclusive? Yes

Arm title Arm A: Nivolumab + Ipilimumab

Arm description:

Participants will receive treatment with nivolumab 3 mg/kg as a 30-minute infusion every 2 weeks and ipilimumab as a 30-minute infusion 1 mg/kg every 6 weeks.

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | No Treatment |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

No Treatment

Arm title Arm B: Nivolumab + Chemotherapy

Arm description:

Participants will receive treatment with nivolumab 240 mg as a 30-minute infusion on Day 1 and Day 15, fluorouracil 800 mg/m²/day as an IV continuous infusion on Day 1 through Day 5 (for 5 days), and cisplatin 80 mg/m² as a 30- to 120-minute infusion on Day 1 of 4-week cycle.

| | |
|---|-----------------|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |

Arm title Arm C: Chemotherapy

Arm description:

Participants will receive treatment with fluorouracil 800 mg/m²/day as an IV continuous infusion from Day 1 through Day 5 (for 5 days), and cisplatin 80 mg/m² as a 30- to 120-minute infusion on Day 1 of 4-week cycle.

| | |
|---|-----------------|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |

| Number of subjects in period 1 | Arm A: Nivolumab + Ipilimumab | Arm B: Nivolumab + Chemotherapy | Arm C: Chemotherapy |
|--|-------------------------------|---------------------------------|---------------------|
| Started | 325 | 321 | 324 |
| Completed | 322 | 310 | 304 |
| Not completed | 3 | 11 | 20 |
| Participant withdrew consent | - | 1 | 12 |
| Other Reasons | 1 | 2 | 1 |
| Participant no longer meets study criteria | - | 4 | 2 |
| Adverse event unrelated to study drug | 1 | 3 | 1 |
| Disease Progression | 1 | 1 | 2 |
| Participant request to discontinue study treatment | - | - | 2 |

Period 2

| | |
|------------------------------|-------------------------|
| Period 2 title | Treatment |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|-------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Arm A: Nivolumab + Ipilimumab |

Arm description:

Participants will receive treatment with nivolumab 3 mg/kg as a 30-minute infusion every 2 weeks and ipilimumab as a 30-minute infusion 1 mg/kg every 6 weeks.

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Ipilimumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

30 minutes infusion 1mg/kg

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

Dosage and administration details:

3 mg/kg as 30 minutes infusion

| | |
|------------------|---------------------------------|
| Arm title | Arm B: Nivolumab + Chemotherapy |
|------------------|---------------------------------|

Arm description:

Participants will receive treatment with nivolumab 240 mg as a 30-minute infusion on Day 1 and Day 15, fluorouracil 800 mg/m²/day as an IV continuous infusion on Day 1 through Day 5 (for 5 days), and cisplatin 80 mg/m² as a 30- to 120-minute infusion on Day 1 of 4-week cycle.

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

| | |
|---|---------------------|
| Investigational medicinal product name | Nivolumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: 240 mg as 30 minutes infusion | |
| Investigational medicinal product name | Cisplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: 80 mg/m ² as a 30- to 120-minute infusion | |
| Investigational medicinal product name | Flurouracil |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: 800 mg/m ² /day as an IV continuous infusion | |
| Arm title | Arm C: Chemotherapy |

Arm description:

Participants will receive treatment with fluorouracil 800 mg/m²/day as an IV continuous infusion from Day 1 through Day 5 (for 5 days), and cisplatin 80 mg/m² as a 30- to 120-minute infusion on Day 1 of 4-week cycle.

| | |
|---|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Cisplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: 80 mg/m ² as a 30- to 120-minute infusion | |
| Investigational medicinal product name | Flurouracil |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: 800 mg/m ² /day as an IV continuous infusion | |

| Number of subjects in period 2 | Arm A: Nivolumab + Ipilimumab | Arm B: Nivolumab + Chemotherapy | Arm C: Chemotherapy |
|---------------------------------------|--------------------------------------|--|----------------------------|
| Started | 322 | 310 | 304 |
| Completed | 28 | 14 | 0 |
| Not completed | 294 | 296 | 304 |
| Adverse event, serious fatal | 6 | 4 | 4 |

| | | | |
|--|-----|-----|-----|
| Participant withdrew consent | 3 | 4 | 12 |
| Study drug toxicity | 59 | 36 | 38 |
| Other Reasons | 10 | 10 | 15 |
| Maximum clinical benefit | 1 | 3 | 4 |
| Pregnancy | 1 | - | - |
| Adverse event unrelated to study drug | 19 | 26 | 11 |
| Disease Progression | 182 | 191 | 199 |
| Participant request to discontinue study treatment | 13 | 22 | 21 |

Baseline characteristics

Reporting groups

| | |
|---|---------------------------------|
| Reporting group title | Arm A: Nivolumab + Ipilimumab |
| Reporting group description: | |
| Participants will receive treatment with nivolumab 3 mg/kg as a 30-minute infusion every 2 weeks and ipilimumab as a 30-minute infusion 1 mg/kg every 6 weeks. | |
| Reporting group title | Arm B: Nivolumab + Chemotherapy |
| Reporting group description: | |
| Participants will receive treatment with nivolumab 240 mg as a 30-minute infusion on Day 1 and Day 15, fluorouracil 800 mg/m ² /day as an IV continuous infusion on Day 1 through Day 5 (for 5 days), and cisplatin 80 mg/m ² as a 30- to 120-minute infusion on Day 1 of 4-week cycle. | |
| Reporting group title | Arm C: Chemotherapy |
| Reporting group description: | |
| Participants will receive treatment with fluorouracil 800 mg/m ² /day as an IV continuous infusion from Day 1 through Day 5 (for 5 days), and cisplatin 80 mg/m ² as a 30- to 120-minute infusion on Day 1 of 4-week cycle. | |

| Reporting group values | Arm A: Nivolumab + Ipilimumab | Arm B: Nivolumab + Chemotherapy | Arm C: Chemotherapy |
|--|-------------------------------|---------------------------------|---------------------|
| Number of subjects | 325 | 321 | 324 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 185 | 167 | 166 |
| From 65-84 years | 140 | 151 | 158 |
| 85 years and over | 0 | 3 | 0 |
| Age Continuous Units: Years | | | |
| arithmetic mean | 62.2 | 63.1 | 63.3 |
| standard deviation | ± 9.1 | ± 9.2 | ± 8.7 |
| Sex: Female, Male Units: Participants | | | |
| Female | 56 | 68 | 49 |
| Male | 269 | 253 | 275 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| White | 79 | 85 | 84 |
| Black or African American | 4 | 1 | 6 |
| American Indian or Alaska Native | 1 | 2 | 1 |
| Asian Indian | 1 | 4 | 3 |
| Chinese | 71 | 74 | 70 |
| Japanese | 131 | 126 | 137 |
| Asian Other | 28 | 23 | 17 |
| Other | 10 | 6 | 6 |

| | | | |
|---|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 970 | | |
| Age categorical Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | | |
| Newborns (0-27 days) | 0 | | |
| Infants and toddlers (28 days-23 months) | 0 | | |
| Children (2-11 years) | 0 | | |
| Adolescents (12-17 years) | 0 | | |
| Adults (18-64 years) | 518 | | |
| From 65-84 years | 449 | | |
| 85 years and over | 3 | | |
| Age Continuous Units: Years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Sex: Female, Male Units: Participants | | | |
| Female | 173 | | |
| Male | 797 | | |
| Race/Ethnicity, Customized Units: Subjects | | | |
| White | 248 | | |
| Black or African American | 11 | | |
| American Indian or Alaska Native | 4 | | |
| Asian Indian | 8 | | |
| Chinese | 215 | | |
| Japanese | 394 | | |
| Asian Other | 68 | | |
| Other | 22 | | |

End points

End points reporting groups

| | |
|---|---------------------------------|
| Reporting group title | Arm A: Nivolumab + Ipilimumab |
| Reporting group description: Participants will receive treatment with nivolumab 3 mg/kg as a 30-minute infusion every 2 weeks and ipilimumab as a 30-minute infusion 1 mg/kg every 6 weeks. | |
| Reporting group title | Arm B: Nivolumab + Chemotherapy |
| Reporting group description: Participants will receive treatment with nivolumab 240 mg as a 30-minute infusion on Day 1 and Day 15, fluorouracil 800 mg/m ² /day as an IV continuous infusion on Day 1 through Day 5 (for 5 days), and cisplatin 80 mg/m ² as a 30- to 120-minute infusion on Day 1 of 4-week cycle. | |
| Reporting group title | Arm C: Chemotherapy |
| Reporting group description: Participants will receive treatment with fluorouracil 800 mg/m ² /day as an IV continuous infusion from Day 1 through Day 5 (for 5 days), and cisplatin 80 mg/m ² as a 30- to 120-minute infusion on Day 1 of 4-week cycle. | |
| Reporting group title | Arm A: Nivolumab + Ipilimumab |
| Reporting group description: Participants will receive treatment with nivolumab 3 mg/kg as a 30-minute infusion every 2 weeks and ipilimumab as a 30-minute infusion 1 mg/kg every 6 weeks. | |
| Reporting group title | Arm B: Nivolumab + Chemotherapy |
| Reporting group description: Participants will receive treatment with nivolumab 240 mg as a 30-minute infusion on Day 1 and Day 15, fluorouracil 800 mg/m ² /day as an IV continuous infusion on Day 1 through Day 5 (for 5 days), and cisplatin 80 mg/m ² as a 30- to 120-minute infusion on Day 1 of 4-week cycle. | |
| Reporting group title | Arm C: Chemotherapy |
| Reporting group description: Participants will receive treatment with fluorouracil 800 mg/m ² /day as an IV continuous infusion from Day 1 through Day 5 (for 5 days), and cisplatin 80 mg/m ² as a 30- to 120-minute infusion on Day 1 of 4-week cycle. | |

Primary: Overall Survival (OS) in participants with tumor cell PD-L1

| | |
|--|---|
| End point title | Overall Survival (OS) in participants with tumor cell PD-L1 |
| End point description: Overall Survival (OS) is defined as the time between the date of randomization and the date of death. For participants without documentation of death, OS will be censored on the last date the subject was known to be alive. | |
| End point type | Primary |
| End point timeframe: From the date of randomization to up to the date of death (up to approximately 20 months) | |

| End point values | Arm A: Nivolumab + Ipilimumab | Arm B: Nivolumab + Chemotherapy | Arm C: Chemotherapy | |
|----------------------------------|-------------------------------------|---------------------------------------|------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 158 | 158 | 157 | |
| Units: Months | | | | |
| median (confidence interval 95%) | 13.70 (11.24 to 17.02) | 15.44 (11.93 to 19.52) | 9.07 (7.69 to 9.95) | |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|--|---|
| Statistical analysis description: Hazard Ratio is Arm A: Nivolumab + Ipilimumab over Arm C: Chemotherapy. | |
| Comparison groups | Arm A: Nivolumab + Ipilimumab v Arm C: Chemotherapy |
| Number of subjects included in analysis | 315 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.001 ^[1] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.64 |
| Confidence interval | |
| level | Other: 98.6 % |
| sides | 2-sided |
| lower limit | 0.46 |
| upper limit | 0.9 |

Notes:

[1] - Log-rank test stratified by ECOG Performance Status (0 vs 1), number of organs with metastases (<= 1 vs. >= 2) as recorded in IRT.

| Statistical analysis title | Statistical Analysis 2 |
|--|---|
| Statistical analysis description: Hazard Ratio is Arm A: Nivolumab + Ipilimumab over Arm C: Chemotherapy. | |
| Comparison groups | Arm A: Nivolumab + Ipilimumab v Arm C: Chemotherapy |
| Number of subjects included in analysis | 315 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.001 ^[2] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.64 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.49 |
| upper limit | 0.84 |

Notes:

[2] - Log-rank test stratified by ECOG Performance Status (0 vs 1), number of organs with metastases (<= 1 vs. >= 2) as recorded in IRT.

| Statistical analysis title | Statistical Analysis 3 |
|---|---|
| Statistical analysis description: Hazard Ratio is Arm B: Nivolumab + Chemotherapy over Arm C: Chemotherapy | |
| Comparison groups | Arm B: Nivolumab + Chemotherapy v Arm C: Chemotherapy |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 315 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 ^[3] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.54 |
| Confidence interval | |
| level | Other: 99.5 % |
| sides | 2-sided |
| lower limit | 0.37 |
| upper limit | 0.8 |

Notes:

[3] - Log-rank test stratified by ECOG Performance Status (0 vs 1), number of organs with metastases (<= 1 vs. >= 2) as recorded in IRT.

| | |
|--|---|
| Statistical analysis title | Statistical Analysis 4 |
| Statistical analysis description: | |
| Hazard Ratio is Arm B: Nivolumab + Chemotherapy over Arm C: Chemotherapy | |
| Comparison groups | Arm B: Nivolumab + Chemotherapy v Arm C: Chemotherapy |
| Number of subjects included in analysis | 315 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 ^[4] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.54 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.41 |
| upper limit | 0.71 |

Notes:

[4] - Log-rank test stratified by ECOG Performance Status (0 vs 1), number of organs with metastases (<= 1 vs. >= 2) as recorded in IRT.

Primary: Progression-free survival (PFS) as assessed by BICR in participants with tumor cell PD-L1

| | |
|---|---|
| End point title | Progression-free survival (PFS) as assessed by BICR in participants with tumor cell PD-L1 |
| End point description: | |
| Progression-free survival (PFS) is defined as the time from randomization to the date of the first documented progressive disease (PD) per Blinded Independent Central Review (BICR) or death due to any cause. Participants who die without a reported prior PD per BICR (and die without start of subsequent therapy) will be considered to have progressed on the date of death. Participants who did not have documented PD per BICR per RECIST1.1 criteria and who did not die, will be censored at the date of the last evaluable tumor assessment on or prior to initiation of the subsequent anti-cancer therapy. Participants who did not have any on-study tumor assessments and did not die (or died after initiation of the subsequent anti-cancer therapy) will be censored at the randomization date. Participants who started any subsequent anti-cancer therapy without a prior reported PD per BICR will be censored at the last tumor assessment on or prior to initiation of the subsequent anti-cancer therapy. | |
| End point type | Primary |

End point timeframe:

From the date of randomization to up to the date of the first documented disease progression or death (up to approximately 9 months)

| End point values | Arm A: Nivolumab + Ipilimumab | Arm B: Nivolumab + Chemotherapy | Arm C: Chemotherapy | |
|----------------------------------|-------------------------------------|---------------------------------------|------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 158 | 158 | 157 | |
| Units: Months | | | | |
| median (confidence interval 95%) | 4.04 (2.40 to 4.93) | 6.93 (5.68 to 8.34) | 4.44 (2.89 to 5.82) | |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|--|---|
| Statistical analysis description: | |
| Hazard Ratio is Arm A: Nivolumab + Ipilimumab over Arm C: Chemotherapy | |
| Comparison groups | Arm A: Nivolumab + Ipilimumab v Arm C: Chemotherapy |
| Number of subjects included in analysis | 315 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.8958 ^[5] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.02 |
| Confidence interval | |
| level | Other: 98.5 % |
| sides | 2-sided |
| lower limit | 0.73 |
| upper limit | 1.43 |

Notes:

[5] - Log-rank test stratified by ECOG Performance Status (0 vs 1), number of organs with metastases (<= 1 vs. >= 2) as recorded in IRT

| Statistical analysis title | Statistical Analysis 4 |
|--|---|
| Statistical analysis description: | |
| Hazard Ratio is Arm B: Nivolumab + Chemotherapy over Arm C: Chemotherapy | |
| Comparison groups | Arm B: Nivolumab + Chemotherapy v Arm C: Chemotherapy |
| Number of subjects included in analysis | 315 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0023 ^[6] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.65 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.49 |
| upper limit | 0.86 |

Notes:

[6] - Log-rank test stratified by ECOG Performance Status (0 vs 1), number of organs with metastases (<= 1 vs. >= 2) as recorded in IRT

| Statistical analysis title | Statistical Analysis 3 |
|--|---|
| Statistical analysis description: | |
| Hazard Ratio is Arm B: Nivolumab + Chemotherapy over Arm C: Chemotherapy | |
| Comparison groups | Arm B: Nivolumab + Chemotherapy v Arm C: Chemotherapy |
| Number of subjects included in analysis | 315 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0023 [7] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.65 |
| Confidence interval | |
| level | Other: 98.5 % |
| sides | 2-sided |
| lower limit | 0.46 |
| upper limit | 0.92 |

Notes:

[7] - Log-rank test stratified by ECOG Performance Status (0 vs 1), number of organs with metastases (<= 1 vs. >= 2) as recorded in IRT

| Statistical analysis title | Statistical Analysis 2 |
|--|---|
| Statistical analysis description: | |
| Hazard Ratio is Arm A: Nivolumab + Ipilimumab over Arm C: Chemotherapy | |
| Comparison groups | Arm A: Nivolumab + Ipilimumab v Arm C: Chemotherapy |
| Number of subjects included in analysis | 315 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.8958 [8] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.78 |
| upper limit | 1.34 |

Notes:

[8] - Log-rank test stratified by ECOG Performance Status (0 vs 1), number of organs with metastases (<= 1 vs. >= 2) as recorded in IRT

Secondary: Overall Survival (OS) in all randomized participants

| | |
|--|--|
| End point title | Overall Survival (OS) in all randomized participants |
| End point description: | |
| Overall Survival (OS) is defined as the time between the date of randomization and the date of death. For participants without documentation of death, OS will be censored on the last date the subject was known to be alive. | |
| End point type | Secondary |
| End point timeframe: | |
| From the date of randomization to up to the date of death (up to approximately 88 months) | |

| End point values | Arm A: Nivolumab + Ipilimumab | Arm B: Nivolumab + Chemotherapy | Arm C: Chemotherapy | |
|----------------------------------|-------------------------------------|---------------------------------------|-----------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 325 | 321 | 324 | |
| Units: Months | | | | |
| median (confidence interval 95%) | 12.747 (11.269 to 15.474) | 13.207 (11.105 to 15.671) | 10.710 (9.396 to 12.090) | |

Statistical analyses

| Statistical analysis title | Statistical Analysis 2 |
|---|---|
| Statistical analysis description: Hazard Ratio is Arm B: Nivolumab + Chemotherapy over Arm C: Chemotherapy | |
| Comparison groups | Arm B: Nivolumab + Chemotherapy v Arm C: Chemotherapy |
| Number of subjects included in analysis | 645 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.77 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.65 |
| upper limit | 0.92 |

| Statistical analysis title | Statistical Analysis 1 |
|---|---|
| Statistical analysis description: Hazard Ratio is Arm A: Nivolumab + Ipilimumab over Arm C: Chemotherapy | |
| Comparison groups | Arm A: Nivolumab + Ipilimumab v Arm C: Chemotherapy |
| Number of subjects included in analysis | 649 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.77 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.65 |
| upper limit | 0.92 |

Secondary: Progression-free survival (PFS) in all randomized participants as assessed by BICR

| | |
|-----------------|--|
| End point title | Progression-free survival (PFS) in all randomized participants as assessed by BICR |
|-----------------|--|

End point description:

Progression-free survival (PFS) is defined as the time from randomization to the date of the first documented progressive disease (PD) per Blinded Independent Central Review (BICR) or death due to any cause. Participants who die without a reported prior PD per BICR (and die without start of subsequent therapy) will be considered to have progressed on the date of death. Participants who did not have documented PD per BICR per RECIST1.1 criteria and who did not die, will be censored at the date of the last evaluable tumor assessment on or prior to initiation of the subsequent anti-cancer therapy. Participants who did not have any on-study tumor assessments and did not die (or died after initiation of the subsequent anti-cancer therapy) will be censored at the randomization date. Participants who started any subsequent anti-cancer therapy without a prior reported PD per BICR will be censored at the last tumor assessment on or prior to initiation of the subsequent anti-cancer therapy.

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

End point timeframe:

From the date of randomization to up to the date of the first documented disease progression or death (up to approximately 88 months)

| End point values | Arm A: Nivolumab + Ipilimumab | Arm B: Nivolumab + Chemotherapy | Arm C: Chemotherapy | |
|----------------------------------|-------------------------------------|---------------------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 325 | 321 | 324 | |
| Units: Months | | | | |
| median (confidence interval 95%) | 2.891 (2.661 to 4.172) | 5.782 (5.520 to 6.998) | 5.618 (4.304 to 5.914) | |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|----------------------------|------------------------|

Statistical analysis description:

Hazard Ratio is Arm B: Nivolumab + Chemotherapy over Arm C: Chemotherapy

| | |
|---|---|
| Comparison groups | Arm B: Nivolumab + Chemotherapy v Arm C: Chemotherapy |
| Number of subjects included in analysis | 645 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.82 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.68 |
| upper limit | 1 |

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

Hazard Ratio is Arm A: Nivolumab + Ipilimumab over Arm C: Chemotherapy

| | |
|---|---|
| Comparison groups | Arm A: Nivolumab + Ipilimumab v Arm C: Chemotherapy |
| Number of subjects included in analysis | 649 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.25 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.04 |
| upper limit | 1.5 |

Secondary: Objective Response Rate (ORR) as assessed by BICR

| | |
|-----------------|---|
| End point title | Objective Response Rate (ORR) as assessed by BICR |
|-----------------|---|

End point description:

Objective response rate (ORR) is defined as the percentage of participants with a best overall response (BOR) of complete response (CR) or partial response (PR). Best overall response (BOR) is defined as the best response designation as determined by BICR, recorded between the date of randomization and the date of objectively documented progression (per RECIST 1.1) or the date of subsequent anti-cancer therapy (including tumor-directed radiotherapy and tumor-directed surgery), whichever occurs first. Partial response is defined as at least a 30% decrease in the sum of diameters of target lesions. Complete response is defined as the disappearance of all target lesions and the reduction of any pathological lymph nodes to <10 mm.

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

End point timeframe:

From the date of randomization to up to the date of objectively documented progression or the date of subsequent anti-cancer therapy, whichever occurs first (up to 88 months)

| End point values | Arm A: Nivolumab + Ipilimumab | Arm B: Nivolumab + Chemotherapy | Arm C: Chemotherapy | |
|--|-------------------------------------|---------------------------------------|------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 325 | 321 | 324 | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Participants with baseline PD-L1 status < 1% | 20.1 (14.3 to 27.1) | 41.7 (34.1 to 49.7) | 33.7 (26.6 to 41.5) | |
| Participants with baseline PD-L1 status ≥ 1% | 35.4 (28.0 to 43.4) | 53.2 (45.1 to 61.1) | 19.9 (13.9 to 27.0) | |
| Participants with baseline PD-L1 status < 5% | 22.3 (16.7 to 28.6) | 44.8 (37.8 to 51.9) | 30.9 (24.7 to 37.7) | |
| Participants with baseline PD-L1 status ≥ 5% | 36.7 (28.1 to 45.9) | 51.7 (42.4 to 60.9) | 20.0 (13.1 to 28.5) | |
| Participants with baseline PD-L1 status < 10% | 23.3 (17.9 to 29.5) | 46.1 (39.4 to 53.0) | 29.3 (23.5 to 35.8) | |
| Participants with baseline PD-L1 status ≥ 10% | 36.9 (27.6 to 47.0) | 50.0 (39.9 to 60.1) | 21.6 (13.9 to 31.2) | |
| Participants with baseline PD-L1 missing | 33.3 (0.8 to 90.6) | 99999 (99999 to 99999) | 0.0 (0.0 to 84.2) | |

| | | | | |
|-----------------------------|---------------------|---------------------|---------------------|--|
| All randomized participants | 27.4 (22.6 to 32.6) | 47.4 (41.8 to 53.0) | 26.9 (22.1 to 32.0) | |
|-----------------------------|---------------------|---------------------|---------------------|--|

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All cause mortality was collected till 88 months and Serious and Non-Serious AEs from first dose (Day 1) to 100 days post last dose (up to 43 months)

Adverse event reporting additional description:

All cause mortality was collected for all the randomized participants and serious and non-serious adverse events were collected for treated population.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 27.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------------------------|
| Reporting group title | Arm A: Nivolumab + Ipilimumab |
|-----------------------|-------------------------------|

Reporting group description:

Participants will receive treatment with nivolumab 3 mg/kg as a 30-minute infusion every 2 weeks and ipilimumab as a 30-minute infusion 1 mg/kg every 6 weeks.

| | |
|-----------------------|---------------------|
| Reporting group title | Arm C: Chemotherapy |
|-----------------------|---------------------|

Reporting group description:

Participants will receive treatment with fluorouracil 800 mg/m²/day as an IV continuous infusion from Day 1 through Day 5 (for 5 days), and cisplatin 80 mg/m² as a 30- to 120-minute infusion on Day 1 of 4-week cycle.

| | |
|-----------------------|---------------------------------|
| Reporting group title | Arm B: Nivolumab + Chemotherapy |
|-----------------------|---------------------------------|

Reporting group description:

Participants will receive treatment with nivolumab 240 mg as a 30-minute infusion on Day 1 and Day 15, fluorouracil 800 mg/m²/day as an IV continuous infusion on Day 1 through Day 5 (for 5 days), and cisplatin 80 mg/m² as a 30- to 120-minute infusion on Day 1 of 4-week cycle.

| Serious adverse events | Arm A: Nivolumab + Ipilimumab | Arm C: Chemotherapy | Arm B: Nivolumab + Chemotherapy |
|---|-------------------------------|---------------------|---------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 243 / 322 (75.47%) | 174 / 304 (57.24%) | 226 / 310 (72.90%) |
| number of deaths (all causes) | 267 | 266 | 262 |
| number of deaths resulting from adverse events | 85 | 75 | 82 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adult T-cell lymphoma/leukaemia | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Benign neoplasm | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-------------------|-------------------|-------------------|
| Cancer pain | | | |
| subjects affected / exposed | 3 / 322 (0.93%) | 1 / 304 (0.33%) | 2 / 310 (0.65%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 59 / 322 (18.32%) | 65 / 304 (21.38%) | 61 / 310 (19.68%) |
| occurrences causally related to treatment / all | 0 / 59 | 0 / 66 | 0 / 63 |
| deaths causally related to treatment / all | 0 / 49 | 0 / 58 | 0 / 49 |
| Lipoma | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Laryngeal cancer | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Hypopharyngeal cancer | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric cancer | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Colorectal cancer | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Colorectal adenoma | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Metastases to bone marrow | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Tumour compression | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour associated fever | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophageal carcinoma | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 0 / 304 (0.00%) | 2 / 310 (0.65%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| Metastatic squamous cell carcinoma | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to meninges | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Metastases to kidney | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Metastases to central nervous system | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour fistulisation | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Tumour haemorrhage | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 3 / 304 (0.99%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Tumour pain | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 4 / 304 (1.32%) | 0 / 310 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Vascular disorders | | | |
| Embolism | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aortic dissection | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Poor venous access | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Haematoma | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertension | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotension | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 3 / 304 (0.99%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypovolaemic shock | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Internal haemorrhage | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Shock | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 2 / 304 (0.66%) | 0 / 310 (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 |
| Shock haemorrhagic | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Venous thrombosis | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Thrombophlebitis | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subclavian vein thrombosis | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Oesophageal operation | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Assisted suicide | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Pregnancy, puerperium and perinatal conditions | | | |
| Pregnancy | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 | 5 / 322 (1.55%) | 1 / 304 (0.33%) | 2 / 310 (0.65%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Catheter site discharge | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Chest pain | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 2 / 310 (0.65%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Complication associated with device | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Death | | | |
| subjects affected / exposed | 5 / 322 (1.55%) | 0 / 304 (0.00%) | 2 / 310 (0.65%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 5 | 0 / 0 | 0 / 2 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 2 / 304 (0.66%) | 2 / 310 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malaise | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 1 / 304 (0.33%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 1 |
| Feeling cold | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 | 3 / 322 (0.93%) | 1 / 304 (0.33%) | 3 / 310 (0.97%) |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 1 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Disease progression | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Nodule | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Pain | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Performance status decreased | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |

| | | | |
|---|------------------|-----------------|-----------------|
| subjects affected / exposed | 14 / 322 (4.35%) | 7 / 304 (2.30%) | 7 / 310 (2.26%) |
| occurrences causally related to treatment / all | 6 / 17 | 1 / 7 | 2 / 9 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sudden death | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 2 / 304 (0.66%) | 2 / 310 (0.65%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 2 |
| Polyp | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Anaphylactic shock | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Aspiration | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 1 / 304 (0.33%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Acquired tracheo-oesophageal fistula | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 2 / 310 (0.65%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atelectasis | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cough | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchostenosis | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchial obstruction | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Dyspnoea | | | |
| subjects affected / exposed | 5 / 322 (1.55%) | 2 / 304 (0.66%) | 2 / 310 (0.65%) |
| occurrences causally related to treatment / all | 1 / 6 | 0 / 2 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Hiccups | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 2 / 304 (0.66%) | 0 / 310 (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 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mediastinal disorder | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung disorder | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Interstitial lung disease | | | |
| subjects affected / exposed | 5 / 322 (1.55%) | 2 / 304 (0.66%) | 2 / 310 (0.65%) |
| occurrences causally related to treatment / all | 6 / 6 | 0 / 2 | 1 / 2 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 0 |
| Immune-mediated lung disease | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Obstructive airways disorder | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophagobronchial fistula | | | |

| | | | |
|---|------------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 4 / 322 (1.24%) | 1 / 304 (0.33%) | 5 / 310 (1.61%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 6 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Pneumomediastinum | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 1 / 304 (0.33%) | 4 / 310 (1.29%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 3 |
| Pulmonary thrombosis | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 3 / 304 (0.99%) | 2 / 310 (0.65%) |
| occurrences causally related to treatment / all | 1 / 2 | 3 / 3 | 0 / 2 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 13 / 322 (4.04%) | 1 / 304 (0.33%) | 6 / 310 (1.94%) |
| occurrences causally related to treatment / all | 13 / 13 | 0 / 1 | 9 / 9 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| Stridor | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Tracheal stenosis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tracheal fistula | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Delirium | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Depression | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Logorrhoea | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Disorientation | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Product issues | | | |
| Device breakage | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Device dislocation | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Device occlusion | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Patient-device incompatibility | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 3 / 322 (0.93%) | 0 / 304 (0.00%) | 0 / 310 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Adjusted calcium increased | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Anticoagulation drug level above therapeutic | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 0 / 304 (0.00%) | 0 / 310 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood sodium decreased | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood creatinine increased | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 3 / 322 (0.93%) | 1 / 304 (0.33%) | 2 / 310 (0.65%) |
| occurrences causally related to treatment / all | 2 / 3 | 1 / 1 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Blood calcium increased | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Blood thyroid stimulating hormone increased | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 1 / 304 (0.33%) | 4 / 310 (1.29%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 2 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Liver function test increased | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 2 / 310 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lipase increased | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Electrocardiogram Q wave abnormal | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Cortisol decreased | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 2 / 304 (0.66%) | 2 / 310 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Urine output decreased | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Anastomotic leak | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Atrio-oesophageal fistula | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Brain contusion | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infusion related reaction | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Lower limb fracture | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Heat illness | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal stoma complication | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 1 / 304 (0.33%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fracture | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fall | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Stoma site discharge | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Radiation oesophagitis | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Overdose | | | |
| subjects affected / exposed | 5 / 322 (1.55%) | 1 / 304 (0.33%) | 0 / 310 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stoma site pain | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Tracheal obstruction | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subdural haematoma | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Acute myocardial infarction | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 322 (0.31%) | 2 / 304 (0.66%) | 0 / 310 (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 |
| Arrhythmia | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 3 / 304 (0.99%) | 0 / 310 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 7 / 7 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arteriospasm coronary | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 1 / 304 (0.33%) | 0 / 310 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Palpitations | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Ventricular fibrillation | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Nervous system disorders | | | |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Facial paralysis | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 infarction | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 1 / 304 (0.33%) | 0 / 310 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Brain stem haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Presyncope | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune-mediated encephalopathy | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Immune-mediated encephalitis | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Hydrocephalus | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Haemorrhagic stroke | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stupor | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subdural hygroma | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Syncope | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal cord compression | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 6 / 322 (1.86%) | 7 / 304 (2.30%) | 5 / 310 (1.61%) |
| occurrences causally related to treatment / all | 0 / 6 | 2 / 8 | 6 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile bone marrow aplasia | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 6 / 322 (1.86%) | 5 / 304 (1.64%) | 7 / 310 (2.26%) |
| occurrences causally related to treatment / all | 0 / 6 | 3 / 5 | 4 / 7 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Disseminated intravascular coagulation | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Immune thrombocytopenia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Leukocytosis | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lymphadenopathy | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Myelosuppression | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 2 / 310 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Splenic haematoma | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Eye disorders | | | |
| Retinal detachment | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye pain | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Cataract | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uveitis | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Vogt-Koyanagi-Harada disease | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 distension | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Abdominal pain | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 322 (0.31%) | 2 / 304 (0.66%) | 3 / 310 (0.97%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 2 / 304 (0.66%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 5 / 322 (1.55%) | 3 / 304 (0.99%) | 7 / 310 (2.26%) |
| occurrences causally related to treatment / all | 2 / 5 | 3 / 3 | 4 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diaphragmatic hernia | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Constipation | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 1 / 304 (0.33%) | 2 / 310 (0.65%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 4 / 322 (1.24%) | 0 / 304 (0.00%) | 5 / 310 (1.61%) |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | 6 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aorto-oesophageal fistula | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ascites | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric perforation | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Gastric fistula | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 2 / 310 (0.65%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enterocolitis | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Enteritis | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Dysphagia | | | |
| subjects affected / exposed | 12 / 322 (3.73%) | 16 / 304 (5.26%) | 21 / 310 (6.77%) |
| occurrences causally related to treatment / all | 0 / 13 | 0 / 20 | 1 / 28 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Duodenal ulcer | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal obstruction | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 5 / 322 (1.55%) | 2 / 304 (0.66%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 5 | 1 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Haematemesis | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 2 / 304 (0.66%) | 0 / 310 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Ileus paralytic | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Ileus | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 1 / 304 (0.33%) | 0 / 310 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematochezia | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Immune-mediated enterocolitis | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 2 / 304 (0.66%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant ascites | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Mechanical ileus | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Melaena | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Nausea | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 5 / 304 (1.64%) | 4 / 310 (1.29%) |
| occurrences causally related to treatment / all | 1 / 2 | 3 / 5 | 3 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Odynophagia | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophageal mass | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophageal haemorrhage | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Oesophageal fistula | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 3 / 304 (0.99%) | 0 / 310 (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 |
| Oesophageal motility disorder | | | |

| | | | |
|---|-----------------|------------------|-----------------|
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophageal obstruction | | | |
| subjects affected / exposed | 3 / 322 (0.93%) | 5 / 304 (1.64%) | 3 / 310 (0.97%) |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 5 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 4 / 322 (1.24%) | 0 / 304 (0.00%) | 0 / 310 (0.00%) |
| occurrences causally related to treatment / all | 3 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophagomediastinal fistula | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophageal-pulmonary fistula | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Oesophageal stenosis | | | |
| subjects affected / exposed | 3 / 322 (0.93%) | 13 / 304 (4.28%) | 9 / 310 (2.90%) |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 13 | 0 / 12 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophageal perforation | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 1 / 304 (0.33%) | 3 / 310 (0.97%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 1 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Oesophageal pain | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 acute | | | |

| | | | |
|---|-----------------|------------------|-----------------|
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Pneumatosis intestinalis | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Rectal perforation | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Small intestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 6 / 310 (1.94%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 5 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 4 / 322 (1.24%) | 2 / 304 (0.66%) | 2 / 310 (0.65%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 5 / 322 (1.55%) | 12 / 304 (3.95%) | 4 / 310 (1.29%) |
| occurrences causally related to treatment / all | 4 / 6 | 9 / 12 | 4 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Autoimmune hepatitis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Bile duct stenosis | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Bile duct stone | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Biliary obstruction | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Hepatitis | | | |
| subjects affected / exposed | 3 / 322 (0.93%) | 0 / 304 (0.00%) | 0 / 310 (0.00%) |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholangitis | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic failure | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 9 / 322 (2.80%) | 1 / 304 (0.33%) | 0 / 310 (0.00%) |
| occurrences causally related to treatment / all | 8 / 9 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Jaundice cholestatic | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune-mediated hepatitis | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Skin and subcutaneous tissue disorders | | | |
| Drug eruption | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Erythema multiforme | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Rash | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 3 / 322 (0.93%) | 0 / 304 (0.00%) | 0 / 310 (0.00%) |
| occurrences causally related to treatment / all | 5 / 5 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subcutaneous emphysema | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute kidney injury | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 4 / 304 (1.32%) | 9 / 310 (2.90%) |
| occurrences causally related to treatment / all | 1 / 2 | 3 / 4 | 6 / 9 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 2 |
| Hydronephrosis | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 1 / 304 (0.33%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 2 / 304 (0.66%) | 3 / 310 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 6 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 | | | |
| Adrenocorticotrophic hormone deficiency | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 8 / 322 (2.48%) | 0 / 304 (0.00%) | 3 / 310 (0.97%) |
| occurrences causally related to treatment / all | 7 / 8 | 0 / 0 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|--|-----------------|-----------------|-----------------|
| Hypercalcaemia of malignancy subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Endocrine disorder subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Hyperthyroidism subjects affected / exposed | 2 / 322 (0.62%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypophysitis subjects affected / exposed | 6 / 322 (1.86%) | 0 / 304 (0.00%) | 0 / 310 (0.00%) |
| occurrences causally related to treatment / all | 6 / 6 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypopituitarism subjects affected / exposed | 7 / 322 (2.17%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 6 / 7 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypothyroidism subjects affected / exposed | 3 / 322 (0.93%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Secondary adrenocortical insufficiency subjects affected / exposed | 2 / 322 (0.62%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Inappropriate antidiuretic hormone secretion subjects affected / exposed | 1 / 322 (0.31%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Thyroiditis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 322 (0.62%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 arthritis | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Gouty arthritis | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Back pain | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthritis | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myositis | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal stenosis | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Osteoarthritis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Osteolysis | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Rhabdomyolysis | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rheumatoid arthritis | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Bacteraemia | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 1 / 304 (0.33%) | 0 / 310 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Device related infection | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 3 / 304 (0.99%) | 2 / 310 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cystitis | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Catheter site infection | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Bacterial infection | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 1 / 304 (0.33%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalitis | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Gastroenteritis bacterial | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Enterocolitis infectious | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalitis bacterial | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| H1N1 influenza | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestine infection | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Lymph gland infection | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Lung abscess | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 1 / 304 (0.33%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 1 / 304 (0.33%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mediastinitis | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oral infection | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meningitis viral | | | |

| | | | |
|---|------------------|------------------|-------------------|
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Otitis media | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Otitis media acute | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 3 / 304 (0.99%) | 0 / 310 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Parotitis | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Pneumonia | | | |
| subjects affected / exposed | 32 / 322 (9.94%) | 20 / 304 (6.58%) | 33 / 310 (10.65%) |
| occurrences causally related to treatment / all | 0 / 35 | 2 / 23 | 6 / 40 |
| deaths causally related to treatment / all | 0 / 6 | 1 / 3 | 1 / 6 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 12 / 322 (3.73%) | 8 / 304 (2.63%) | 6 / 310 (1.94%) |
| occurrences causally related to treatment / all | 0 / 14 | 0 / 8 | 0 / 8 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Pneumonia bacterial | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 4 / 322 (1.24%) | 2 / 304 (0.66%) | 0 / 310 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia pseudomonal | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Postoperative wound infection | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Pulmonary sepsis | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 tract infection | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 3 / 310 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| Sepsis | | | |
| subjects affected / exposed | 4 / 322 (1.24%) | 3 / 304 (0.99%) | 3 / 310 (0.97%) |
| occurrences causally related to treatment / all | 0 / 4 | 1 / 3 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 2 | 1 / 1 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 1 / 304 (0.33%) | 0 / 310 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Stoma site cellulitis | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Stoma site infection | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urethritis | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 3 / 310 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Vascular device infection | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 2 / 304 (0.66%) | 0 / 310 (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 |
| Viral infection | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Metabolism and nutrition disorders | | | |
| Cachexia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Decreased appetite | | | |
| subjects affected / exposed | 9 / 322 (2.80%) | 7 / 304 (2.30%) | 4 / 310 (1.29%) |
| occurrences causally related to treatment / all | 2 / 9 | 2 / 7 | 6 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dehydration | | | |
| subjects affected / exposed | 9 / 322 (2.80%) | 6 / 304 (1.97%) | 4 / 310 (1.29%) |
| occurrences causally related to treatment / all | 3 / 10 | 4 / 6 | 2 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetes mellitus | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Electrolyte imbalance | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Fulminant type 1 diabetes mellitus | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gout | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypercalcaemia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 5 / 322 (1.55%) | 4 / 304 (1.32%) | 4 / 310 (1.29%) |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 4 | 1 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 4 / 322 (1.24%) | 1 / 304 (0.33%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemic hyperosmolar nonketotic syndrome | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Hypophagia | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 304 (0.33%) | 0 / 310 (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 |
| Hyponatraemia | | | |
| subjects affected / exposed | 6 / 322 (1.86%) | 4 / 304 (1.32%) | 4 / 310 (1.29%) |
| occurrences causally related to treatment / all | 6 / 7 | 4 / 5 | 4 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 2 / 304 (0.66%) | 4 / 310 (1.29%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 3 | 2 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypocalcaemia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Hypernatraemia | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 304 (0.00%) | 0 / 310 (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 |
| Type 1 diabetes mellitus | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 0 / 304 (0.00%) | 2 / 310 (0.65%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malnutrition | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 1 / 304 (0.33%) | 1 / 310 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Arm A: Nivolumab + Ipilimumab | Arm C: Chemotherapy | Arm B: Nivolumab + Chemotherapy |
|--|----------------------------------|------------------------|------------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 301 / 322 (93.48%) | 288 / 304 (94.74%) | 307 / 310 (99.03%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cancer pain | | | |
| subjects affected / exposed | 18 / 322 (5.59%) | 19 / 304 (6.25%) | 15 / 310 (4.84%) |
| occurrences (all) | 19 | 19 | 18 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 9 / 322 (2.80%) | 22 / 304 (7.24%) | 24 / 310 (7.74%) |
| occurrences (all) | 15 | 25 | 37 |
| Hypotension | | | |

| | | | |
|---|------------------------|------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 11 / 322 (3.42%) 11 | 16 / 304 (5.26%) 19 | 13 / 310 (4.19%) 15 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 56 / 322 (17.39%) | 63 / 304 (20.72%) | 83 / 310 (26.77%) |
| occurrences (all) | 69 | 98 | 121 |
| Asthenia | | | |
| subjects affected / exposed | 25 / 322 (7.76%) | 26 / 304 (8.55%) | 24 / 310 (7.74%) |
| occurrences (all) | 29 | 38 | 52 |
| Infusion site extravasation | | | |
| subjects affected / exposed | 6 / 322 (1.86%) | 20 / 304 (6.58%) | 15 / 310 (4.84%) |
| occurrences (all) | 6 | 28 | 24 |
| Malaise | | | |
| subjects affected / exposed | 27 / 322 (8.39%) | 55 / 304 (18.09%) | 59 / 310 (19.03%) |
| occurrences (all) | 36 | 85 | 108 |
| Pyrexia | | | |
| subjects affected / exposed | 76 / 322 (23.60%) | 48 / 304 (15.79%) | 65 / 310 (20.97%) |
| occurrences (all) | 131 | 59 | 84 |
| Oedema peripheral | | | |
| subjects affected / exposed | 32 / 322 (9.94%) | 25 / 304 (8.22%) | 45 / 310 (14.52%) |
| occurrences (all) | 37 | 52 | 67 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 4 / 322 (1.24%) | 30 / 304 (9.87%) | 37 / 310 (11.94%) |
| occurrences (all) | 4 | 41 | 70 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Productive cough | | | |
| subjects affected / exposed | 14 / 322 (4.35%) | 16 / 304 (5.26%) | 14 / 310 (4.52%) |
| occurrences (all) | 15 | 18 | 17 |
| Pneumonitis | | | |
| subjects affected / exposed | 17 / 322 (5.28%) | 6 / 304 (1.97%) | 20 / 310 (6.45%) |
| occurrences (all) | 17 | 6 | 21 |
| Hiccups | | | |
| subjects affected / exposed | 12 / 322 (3.73%) | 63 / 304 (20.72%) | 53 / 310 (17.10%) |
| occurrences (all) | 15 | 124 | 115 |
| Dyspnoea | | | |

| | | | |
|--------------------------------------|-------------------|-------------------|-------------------|
| subjects affected / exposed | 24 / 322 (7.45%) | 11 / 304 (3.62%) | 14 / 310 (4.52%) |
| occurrences (all) | 27 | 11 | 20 |
| Cough | | | |
| subjects affected / exposed | 40 / 322 (12.42%) | 37 / 304 (12.17%) | 44 / 310 (14.19%) |
| occurrences (all) | 52 | 42 | 51 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 33 / 322 (10.25%) | 40 / 304 (13.16%) | 54 / 310 (17.42%) |
| occurrences (all) | 37 | 48 | 63 |
| Investigations | | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 12 / 322 (3.73%) | 61 / 304 (20.07%) | 75 / 310 (24.19%) |
| occurrences (all) | 20 | 131 | 188 |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 8 / 322 (2.48%) | 9 / 304 (2.96%) | 16 / 310 (5.16%) |
| occurrences (all) | 14 | 13 | 39 |
| Creatinine renal clearance decreased | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 9 / 304 (2.96%) | 20 / 310 (6.45%) |
| occurrences (all) | 0 | 11 | 24 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 13 / 322 (4.04%) | 40 / 304 (13.16%) | 41 / 310 (13.23%) |
| occurrences (all) | 17 | 60 | 71 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 19 / 322 (5.90%) | 10 / 304 (3.29%) | 22 / 310 (7.10%) |
| occurrences (all) | 23 | 11 | 24 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 48 / 322 (14.91%) | 12 / 304 (3.95%) | 28 / 310 (9.03%) |
| occurrences (all) | 61 | 17 | 32 |
| Platelet count decreased | | | |
| subjects affected / exposed | 13 / 322 (4.04%) | 36 / 304 (11.84%) | 46 / 310 (14.84%) |
| occurrences (all) | 18 | 73 | 95 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 44 / 322 (13.66%) | 13 / 304 (4.28%) | 26 / 310 (8.39%) |
| occurrences (all) | 60 | 18 | 35 |
| Weight decreased | | | |

| | | | |
|--|--------------------------|---------------------------|---------------------------|
| subjects affected / exposed occurrences (all) | 43 / 322 (13.35%) 51 | 35 / 304 (11.51%) 44 | 41 / 310 (13.23%) 51 |
| Weight increased subjects affected / exposed occurrences (all) | 6 / 322 (1.86%) 8 | 14 / 304 (4.61%) 25 | 25 / 310 (8.06%) 41 |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 12 / 322 (3.73%) 30 | 41 / 304 (13.49%) 70 | 58 / 310 (18.71%) 141 |
| Nervous system disorders | | | |
| Headache subjects affected / exposed occurrences (all) | 26 / 322 (8.07%) 29 | 16 / 304 (5.26%) 17 | 27 / 310 (8.71%) 33 |
| Dizziness subjects affected / exposed occurrences (all) | 17 / 322 (5.28%) 19 | 29 / 304 (9.54%) 38 | 18 / 310 (5.81%) 31 |
| Dysgeusia subjects affected / exposed occurrences (all) | 10 / 322 (3.11%) 10 | 19 / 304 (6.25%) 25 | 23 / 310 (7.42%) 30 |
| Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 5 / 322 (1.55%) 7 | 28 / 304 (9.21%) 29 | 31 / 310 (10.00%) 32 |
| Neuropathy peripheral subjects affected / exposed occurrences (all) | 2 / 322 (0.62%) 2 | 15 / 304 (4.93%) 16 | 22 / 310 (7.10%) 26 |
| Blood and lymphatic system disorders | | | |
| Neutropenia subjects affected / exposed occurrences (all) | 6 / 322 (1.86%) 12 | 23 / 304 (7.57%) 38 | 38 / 310 (12.26%) 70 |
| Anaemia subjects affected / exposed occurrences (all) | 84 / 322 (26.09%) 122 | 108 / 304 (35.53%) 168 | 156 / 310 (50.32%) 265 |
| Gastrointestinal disorders | | | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 16 / 322 (4.97%) 17 | 13 / 304 (4.28%) 16 | 22 / 310 (7.10%) 25 |
| Abdominal pain | | | |

| | | | |
|--|-------------------|--------------------|--------------------|
| subjects affected / exposed | 22 / 322 (6.83%) | 18 / 304 (5.92%) | 23 / 310 (7.42%) |
| occurrences (all) | 24 | 22 | 29 |
| Constipation | | | |
| subjects affected / exposed | 87 / 322 (27.02%) | 138 / 304 (45.39%) | 142 / 310 (45.81%) |
| occurrences (all) | 104 | 203 | 216 |
| Diarrhoea | | | |
| subjects affected / exposed | 84 / 322 (26.09%) | 63 / 304 (20.72%) | 98 / 310 (31.61%) |
| occurrences (all) | 114 | 116 | 171 |
| Vomiting | | | |
| subjects affected / exposed | 53 / 322 (16.46%) | 60 / 304 (19.74%) | 77 / 310 (24.84%) |
| occurrences (all) | 68 | 95 | 132 |
| Stomatitis | | | |
| subjects affected / exposed | 34 / 322 (10.56%) | 75 / 304 (24.67%) | 100 / 310 (32.26%) |
| occurrences (all) | 43 | 148 | 197 |
| Nausea | | | |
| subjects affected / exposed | 88 / 322 (27.33%) | 172 / 304 (56.58%) | 207 / 310 (66.77%) |
| occurrences (all) | 119 | 378 | 452 |
| Dysphagia | | | |
| subjects affected / exposed | 39 / 322 (12.11%) | 31 / 304 (10.20%) | 42 / 310 (13.55%) |
| occurrences (all) | 44 | 37 | 52 |
| Hepatobiliary disorders | | | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 17 / 322 (5.28%) | 1 / 304 (0.33%) | 3 / 310 (0.97%) |
| occurrences (all) | 22 | 1 | 3 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 10 / 322 (3.11%) | 42 / 304 (13.82%) | 42 / 310 (13.55%) |
| occurrences (all) | 10 | 42 | 42 |
| Dry skin | | | |
| subjects affected / exposed | 18 / 322 (5.59%) | 12 / 304 (3.95%) | 13 / 310 (4.19%) |
| occurrences (all) | 19 | 12 | 13 |
| Pruritus | | | |
| subjects affected / exposed | 59 / 322 (18.32%) | 20 / 304 (6.58%) | 38 / 310 (12.26%) |
| occurrences (all) | 71 | 21 | 52 |
| Rash | | | |

| | | | |
|---|--------------------------|------------------------|-------------------------|
| subjects affected / exposed occurrences (all) | 75 / 322 (23.29%) 100 | 22 / 304 (7.24%) 27 | 43 / 310 (13.87%) 52 |
| Rash maculo-papular subjects affected / exposed occurrences (all) | 18 / 322 (5.59%) 20 | 3 / 304 (0.99%) 3 | 8 / 310 (2.58%) 9 |
| Renal and urinary disorders Renal impairment subjects affected / exposed occurrences (all) | 2 / 322 (0.62%) 2 | 17 / 304 (5.59%) 21 | 12 / 310 (3.87%) 13 |
| Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all) | 44 / 322 (13.66%) 45 | 1 / 304 (0.33%) 1 | 23 / 310 (7.42%) 24 |
| Hyperthyroidism subjects affected / exposed occurrences (all) | 20 / 322 (6.21%) 22 | 1 / 304 (0.33%) 1 | 7 / 310 (2.26%) 8 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 28 / 322 (8.70%) 33 | 13 / 304 (4.28%) 15 | 19 / 310 (6.13%) 20 |
| Back pain subjects affected / exposed occurrences (all) | 21 / 322 (6.52%) 22 | 15 / 304 (4.93%) 15 | 12 / 310 (3.87%) 15 |
| Infections and infestations Pneumonia subjects affected / exposed occurrences (all) | 37 / 322 (11.49%) 41 | 30 / 304 (9.87%) 32 | 33 / 310 (10.65%) 39 |
| Metabolism and nutrition disorders Hypocalcaemia subjects affected / exposed occurrences (all) | 9 / 322 (2.80%) 15 | 5 / 304 (1.64%) 8 | 18 / 310 (5.81%) 28 |
| Hypoalbuminaemia subjects affected / exposed occurrences (all) | 34 / 322 (10.56%) 54 | 20 / 304 (6.58%) 28 | 25 / 310 (8.06%) 34 |
| Hyperkalaemia | | | |

| | | | |
|-----------------------------|-------------------|--------------------|--------------------|
| subjects affected / exposed | 12 / 322 (3.73%) | 22 / 304 (7.24%) | 20 / 310 (6.45%) |
| occurrences (all) | 13 | 33 | 27 |
| Hypercalcaemia | | | |
| subjects affected / exposed | 11 / 322 (3.42%) | 9 / 304 (2.96%) | 20 / 310 (6.45%) |
| occurrences (all) | 13 | 12 | 24 |
| Decreased appetite | | | |
| subjects affected / exposed | 70 / 322 (21.74%) | 156 / 304 (51.32%) | 161 / 310 (51.94%) |
| occurrences (all) | 88 | 296 | 299 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 14 / 322 (4.35%) | 4 / 304 (1.32%) | 17 / 310 (5.48%) |
| occurrences (all) | 16 | 8 | 19 |
| Hyponatraemia | | | |
| subjects affected / exposed | 32 / 322 (9.94%) | 36 / 304 (11.84%) | 55 / 310 (17.74%) |
| occurrences (all) | 48 | 49 | 77 |
| Hypokalaemia | | | |
| subjects affected / exposed | 34 / 322 (10.56%) | 30 / 304 (9.87%) | 44 / 310 (14.19%) |
| occurrences (all) | 55 | 56 | 70 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 21 December 2016 | Expansion of the esophageal cohort into a 3-arm randomized Phase 3 study in first line squamous esophageal cancer. The study now includes a nivolumab plus chemotherapy arm (fluorouracil and cisplatin) and a chemotherapy alone arm in addition to the existing nivolumab and ipilimumab arm. The gastric cohort was removed. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported