



Clinical trial results:

A Phase 3, randomized, double-blind trial of pembrolizumab (MK-3475) with or without lenvatinib (E7080/MK-7902) in participants with treatment-naïve, metastatic nonsmall cell lung cancer (NSCLC) whose tumors have a tumor proportion score (TPS) greater than or equal to 1% (LEAP-007)

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2018-003794-98 |
| Trial protocol | EE HU PL IT |
| Global end of trial date | 24 April 2024 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 11 April 2025 |
| First version publication date | 11 April 2025 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | 7902-007 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|--|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03829332 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Eisai Protocol Number: E7080-G000-314, MSD: LEAP-007, APIC-CTI: 194670 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Merck Sharp & Dohme LLC |
| Sponsor organisation address | 126 East Lincoln Avenue, P.O. Box 2000, Rahway, NJ, United States, 07065 |
| Public contact | Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@msd.com |
| Scientific contact | Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@msd.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 | 24 April 2024 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 19 May 2021 |
| Global end of trial reached? | Yes |
| Global end of trial date | 24 April 2024 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to assess the safety and efficacy of pembrolizumab (MK-3475) combined with lenvatinib (MK-7902/E7080) compared to pembrolizumab alone (with placebo for lenvatinib) in treatment-naïve adults with no prior systemic therapy for their metastatic non-small cell lung cancer (NSCLC) whose tumors have a programmed cell death-ligand 1 (PD-L1) Tumor Proportion Score (TPS) greater than or equal to 1%.

The primary study hypotheses are that: 1) the combination of pembrolizumab and lenvatinib is superior to pembrolizumab alone as assessed by Progression-free Survival (PFS) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1); and 2) the combination of pembrolizumab and lenvatinib is superior to pembrolizumab alone as assessed by Overall Survival (OS).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 13 March 2019 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--|
| Country: Number of subjects enrolled | Australia: 5 |
| Country: Number of subjects enrolled | Canada: 15 |
| Country: Number of subjects enrolled | China: 80 |
| Country: Number of subjects enrolled | Colombia: 9 |
| Country: Number of subjects enrolled | Estonia: 9 |
| Country: Number of subjects enrolled | France: 17 |
| Country: Number of subjects enrolled | Hungary: 68 |
| Country: Number of subjects enrolled | Israel: 20 |
| Country: Number of subjects enrolled | Italy: 34 |
| Country: Number of subjects enrolled | Japan: 41 |
| Country: Number of subjects enrolled | Korea, Democratic People's Republic of: 31 |
| Country: Number of subjects enrolled | Malaysia: 36 |
| Country: Number of subjects enrolled | Mexico: 41 |
| Country: Number of subjects enrolled | Poland: 31 |
| Country: Number of subjects enrolled | Russian Federation: 38 |

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Taiwan: 19 |
| Country: Number of subjects enrolled | Türkiye: 43 |
| Country: Number of subjects enrolled | Ukraine: 65 |
| Country: Number of subjects enrolled | United States: 21 |
| Worldwide total number of subjects | 623 |
| EEA total number of subjects | 159 |

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) | 279 |
| From 65 to 84 years | 341 |
| 85 years and over | 3 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Of the 623 total participants randomized in the MK-7902-007 global study, 80 were also randomized in the China extension study for MK-7902-007 (NCT04676412).

Period 1

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

Arms

| | |
|------------------------------|----------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Pembrolizumab + Lenvatinib |

Arm description:

Participants received pembrolizumab 200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 35 administrations (up to approximately 2 years) PLUS lenvatinib 20 mg via oral capsule once daily (QD) on Days 1-21 of each 3-week cycle until progressive disease or unacceptable toxicity. As of 30-Jul-2021, participants discontinued lenvatinib and participants who remained on treatment received open-label pembrolizumab only at same dose and schedule.

| | |
|--|------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Lenvatinib |
| Investigational medicinal product code | |
| Other name | MK-7902 E7080 LENVIMA® |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

20 mg via oral capsule once daily (QD) on Days 1-21 of each 3-week cycle until progressive disease or unacceptable toxicity.

| | |
|--|-----------------------|
| Investigational medicinal product name | Pembrolizumab |
| Investigational medicinal product code | |
| Other name | MK-3475 KEYTRUDA® |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

200 mg via IV infusion on Day 1 of each 3-week cycle for up to 35 administrations (up to approximately 2 years)

| | |
|------------------|-------------------------|
| Arm title | Pembrolizumab + Placebo |
|------------------|-------------------------|

Arm description:

Participants received pembrolizumab 200 mg via IV infusion on Day 1 of each 3-week cycle for up to 35 administrations (up to approximately 2 years) PLUS placebo for lenvatinib via oral capsule QD on Days 1-21 of each 3-week cycle until progressive disease or unacceptable toxicity. As of 30-Jul-2021, participants discontinued placebo and participants who remained on treatment received open-label pembrolizumab only at same dose and schedule.

| | |
|--|------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Placebo for lenvatinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

oral capsule QD on Days 1-21 of each
3-week cycle until progressive disease
or unacceptable toxicity

| | |
|--|-----------------------|
| Investigational medicinal product name | Pembrolizumab |
| Investigational medicinal product code | |
| Other name | MK-3475 KEYTRUDA® |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

200 mg via IV infusion on Day 1 of
each 3-week cycle for up to 35
administrations (up to approximately 2
years)

| Number of subjects in period 1 | Pembrolizumab + Lenvatinib | Pembrolizumab + Placebo |
|---------------------------------------|-------------------------------|----------------------------|
| Started | 309 | 314 |
| Treated | 309 | 312 |
| Completed | 0 | 0 |
| Not completed | 309 | 314 |
| Physician decision | 1 | - |
| Consent withdrawn by subject | 11 | 9 |
| Death | 225 | 230 |
| Sponsor Decision | 71 | 72 |
| Lost to follow-up | 1 | 3 |

Baseline characteristics

Reporting groups

| | |
|---|----------------------------|
| Reporting group title | Pembrolizumab + Lenvatinib |
| Reporting group description: | |
| Participants received pembrolizumab 200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 35 administrations (up to approximately 2 years) PLUS lenvatinib 20 mg via oral capsule once daily (QD) on Days 1-21 of each 3-week cycle until progressive disease or unacceptable toxicity. As of 30-Jul-2021, participants discontinued lenvatinib and participants who remained on treatment received open-label pembrolizumab only at same dose and schedule. | |
| Reporting group title | Pembrolizumab + Placebo |
| Reporting group description: | |
| Participants received pembrolizumab 200 mg via IV infusion on Day 1 of each 3-week cycle for up to 35 administrations (up to approximately 2 years) PLUS placebo for lenvatinib via oral capsule QD on Days 1-21 of each 3-week cycle until progressive disease or unacceptable toxicity. As of 30-Jul-2021, participants discontinued placebo and participants who remained on treatment received open-label pembrolizumab only at same dose and schedule. | |

| Reporting group values | Pembrolizumab + Lenvatinib | Pembrolizumab + Placebo | Total |
|--|----------------------------|-------------------------|-------|
| Number of subjects | 309 | 314 | 623 |
| Age categorical Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Newborns (0-27 days) | | | |
| Infants and toddlers (28 days-23 months) | | | |
| Children (2-11 years) | | | |
| Adolescents (12-17 years) | | | |
| Adults (18-64 years) | | | |
| From 65-84 years | | | |
| 85 years and over | | | |
| Age Continuous Units: years | | | |
| arithmetic mean | 64.6 | 65.4 | - |
| standard deviation | ± 9.6 | ± 8.8 | |
| Sex: Female, Male Units: Participants | | | |
| Female | 79 | 90 | 169 |
| Male | 230 | 224 | 454 |
| Race (NIH/OMB) Units: Subjects | | | |
| American Indian or Alaska Native | 7 | 3 | 10 |
| Asian | 103 | 104 | 207 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 0 | 1 | 1 |
| White | 188 | 193 | 381 |
| More than one race | 3 | 3 | 6 |
| Unknown or Not Reported | 8 | 10 | 18 |
| Ethnicity (NIH/OMB) | | | |

| | | | |
|---|-----|-----|-----|
| Units: Subjects | | | |
| Hispanic or Latino | 32 | 30 | 62 |
| Not Hispanic or Latino | 266 | 269 | 535 |
| Unknown or Not Reported | 11 | 15 | 26 |
| Eastern Cooperative Oncology Group (ECOG) Performance Status | | | |
| Randomization of participants in the study was stratified by an ECOG Performance Status of 0 (Fully active, able to carry on all pre-disease performance without restriction) or 1 (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature). | | | |
| Units: Subjects | | | |
| ECOG = 0 | 110 | 108 | 218 |
| ECOG = 1 | 199 | 206 | 405 |
| Programmed Cell Death Ligand 1 (PD-L1) Status at Baseline | | | |
| Participants were assessed for their PD-L1 tumor expression level by immunohistochemistry assay using tumor tissue from a newly obtained biopsy. Randomization of participants in the study was stratified by PD-L1 tumor proportion score (TPS) at baseline (1-49% or $\geq 50\%$). Higher percentages of PD-L1 TPS staining correspond to higher positivity of PD-L1 on a tumor. | | | |
| Units: Subjects | | | |
| TPS = 1-49% | 172 | 175 | 347 |
| TPS = $\geq 50\%$ | 137 | 139 | 276 |
| Geographic Region | | | |
| Randomization of participants in this study was stratified by geographic region of the enrolling site (East Asia or non-East Asia). | | | |
| Units: Subjects | | | |
| East Asia | 103 | 104 | 207 |
| Non-East Asia | 206 | 210 | 416 |

End points

End points reporting groups

| | |
|-----------------------|----------------------------|
| Reporting group title | Pembrolizumab + Lenvatinib |
|-----------------------|----------------------------|

Reporting group description:

Participants received pembrolizumab 200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 35 administrations (up to approximately 2 years) PLUS lenvatinib 20 mg via oral capsule once daily (QD) on Days 1-21 of each 3-week cycle until progressive disease or unacceptable toxicity. As of 30-Jul-2021, participants discontinued lenvatinib and participants who remained on treatment received open-label pembrolizumab only at same dose and schedule.

| | |
|-----------------------|-------------------------|
| Reporting group title | Pembrolizumab + Placebo |
|-----------------------|-------------------------|

Reporting group description:

Participants received pembrolizumab 200 mg via IV infusion on Day 1 of each 3-week cycle for up to 35 administrations (up to approximately 2 years) PLUS placebo for lenvatinib via oral capsule QD on Days 1-21 of each 3-week cycle until progressive disease or unacceptable toxicity. As of 30-Jul-2021, participants discontinued placebo and participants who remained on treatment received open-label pembrolizumab only at same dose and schedule.

Primary: Progression-free Survival (PFS) as Assessed by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

| | |
|-----------------|--|
| End point title | Progression-free Survival (PFS) as Assessed by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) |
|-----------------|--|

End point description:

PFS was defined as the time from date of randomization to the date of the first documentation of progressive disease (PD) or death from any cause, whichever occurred first. Per RECIST 1.1, PD was defined as $\geq 20\%$ increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of ≥ 5 mm. The appearance of one or more new lesions was also considered PD. Data are from the product-limit (Kaplan-Meier) method for censored data. PFS as assessed by blinded independent central review (BICR) per RECIST 1.1 was presented. The analysis population consisted of all randomized participants.

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

End point timeframe:

Up to approximately 25 months

| End point values | Pembrolizumab + Lenvatinib | Pembrolizumab + Placebo | | |
|----------------------------------|----------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 309 | 314 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 6.6 (6.1 to 8.2) | 4.2 (4.1 to 6.2) | | |

Statistical analyses

| | |
|----------------------------|--------------|
| Statistical analysis title | Hazard Ratio |
|----------------------------|--------------|

Statistical analysis description:

Hazard ratio (HR) and 95% confidence interval (CI) were calculated using Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by ECOG performance status (0 versus 1), geographic region of the enrolling site (East Asia versus non-East Asia), and baseline PD-L1 Status (1% to 49% versus $\geq 50\%$).

| | |
|---|--|
| Comparison groups | Pembrolizumab + Lenvatinib v Pembrolizumab + Placebo |
| Number of subjects included in analysis | 623 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.00624 |
| Method | Stratified Log Rank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.78 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.64 |
| upper limit | 0.95 |

Primary: Overall Survival (OS)

| | |
|--|-----------------------|
| End point title | Overall Survival (OS) |
| End point description: | |
| OS was defined as the time from date of randomization to date of death from any cause. OS was presented. The analysis population consisted of all randomized participants. | |
| End point type | Primary |
| End point timeframe: | |
| Up to approximately 25 months | |

| End point values | Pembrolizumab + Lenvatinib | Pembrolizumab + Placebo | | |
|----------------------------------|----------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 309 | 314 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 14.1 (11.4 to 19.0) | 16.4 (12.6 to 20.6) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Hazard Ratio |
| Statistical analysis description: | |
| HR and 95% CI were calculated using Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by ECOG performance status (0 versus 1), geographic region of the enrolling site (East Asia versus non-East Asia), and baseline PD-L1 Status (1% to 49% versus ≥50%). | |
| Comparison groups | Pembrolizumab + Lenvatinib v Pembrolizumab + Placebo |

| | |
|---|---------------------|
| Number of subjects included in analysis | 623 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.79744 |
| Method | Stratified Log Rank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.87 |
| upper limit | 1.39 |

Secondary: Change from Baseline in European Organization for Research and Treatment (EORTC) Quality of Life Questionnaire-Core30 (QLQ-C30) Combined Global Health Status/Quality of Life (Items 29 & 30) Scale Combined Score

| | |
|-----------------|--|
| End point title | Change from Baseline in European Organization for Research and Treatment (EORTC) Quality of Life Questionnaire-Core30 (QLQ-C30) Combined Global Health Status/Quality of Life (Items 29 & 30) Scale Combined Score |
|-----------------|--|

End point description:

EORTC QLQ-C30 is a questionnaire to assess the overall quality of life (QoL) of cancer patients. Participant responses to questions regarding Global Health Status (GHS; "How would you rate your overall health during the past week?") and QoL ("How would you rate your overall quality of life during the past week?") are scored on a 7-point scale (1= Very poor to 7=Excellent). The combined score of GHS (Item 29) and QoL (Item 30) is computed by averaging the raw scores of the 2 items and then applying a linear transformation to standardize the average score, so that the combined scores range from 0-100. A higher score indicates a better outcome. Per protocol, the change from baseline in GHS and QoL combined score was presented. All randomized participants who have received at least one dose of the study intervention and had at least one EORTC QLQ-C30 assessment data available for this outcome measure.

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

End point timeframe:

Baseline and Week 21

| End point values | Pembrolizumab + Lenvatinib | Pembrolizumab + Placebo | | |
|--|----------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 309 | 308 | | |
| Units: Score on a scale | | | | |
| least squares mean (confidence interval 95%) | -1.48 (-4.09 to 1.13) | 2.42 (-0.24 to 5.08) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Difference in LS Means |
| Comparison groups | Pembrolizumab + Lenvatinib v Pembrolizumab + Placebo |

| | |
|---|--|
| Number of subjects included in analysis | 617 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0262 |
| Method | Constrained longitudinal data analysis |
| Parameter estimate | Difference in Least Square (LS) Means |
| Point estimate | -3.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.34 |
| upper limit | -0.47 |

Secondary: Number of Participants Who Discontinued Study Treatment Due to an Adverse Event (AE)

| | |
|-----------------|--|
| End point title | Number of Participants Who Discontinued Study Treatment Due to an Adverse Event (AE) |
|-----------------|--|

End point description:

An AE was any untoward medical occurrence in a participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. The number of participants who discontinued study treatment due to an AE were reported. The analysis population consisted of all randomized participants.

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

End point timeframe:

Through last dose of study treatment (Up to approximately 24 months)

| End point values | Pembrolizumab + Lenvatinib | Pembrolizumab + Placebo | | |
|-----------------------------|----------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 309 | 312 | | |
| Units: Participants | 98 | 41 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Experienced an Adverse Event (AE)

| | |
|-----------------|--|
| End point title | Number of Participants Who Experienced an Adverse Event (AE) |
|-----------------|--|

End point description:

An AE was any untoward medical occurrence in a participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. The number of participants who experienced an AE were reported. The analysis population consisted of all randomized participants.

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

End point timeframe:

Through 90 days post last dose of study treatment (Up to approximately 27 months)

| End point values | Pembrolizumab + Lenvatinib | Pembrolizumab + Placebo | | |
|-----------------------------|----------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 309 | 312 | | |
| Units: Participants | 306 | 294 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR) as Assessed by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

| | |
|------------------------|--|
| End point title | Objective Response Rate (ORR) as Assessed by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) |
| End point description: | ORR was defined as the percentage of participants in the analysis population who have a Complete Response (CR: Disappearance of all target lesions) or a Partial Response (PR: At least a 30% decrease in the sum of diameters of target lesions) per RECIST 1.1. ORR as assessed by BICR per RECIST 1.1 is presented. The analysis population consisted of all randomized participants. |
| End point type | Secondary |
| End point timeframe: | Up to approximately 25 months |

| End point values | Pembrolizumab + Lenvatinib | Pembrolizumab + Placebo | | |
|-----------------------------------|----------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 309 | 314 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 40.5 (34.9 to 46.2) | 27.7 (22.8 to 33.0) | | |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | Percent Difference |
| Statistical analysis description: | Percent difference and 95% CI were calculated using Miettinen & Nurminen method stratified by ECOG performance status (0 versus 1), geographic region of the enrolling site (East Asia versus non-East Asia), and baseline PD-L1 Status (1% to 49% versus ≥50%). |
| Comparison groups | Pembrolizumab + Lenvatinib v Pembrolizumab + Placebo |

| | |
|---|---------------------------------|
| Number of subjects included in analysis | 623 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.00037 |
| Method | Stratified Miettinen & Nurminen |
| Parameter estimate | Percent Difference |
| Point estimate | 12.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 5.4 |
| upper limit | 20.1 |

Secondary: Change from Baseline in Dyspnea (EORTC QLQ-C30 Item 8) Score

| | |
|-----------------|--|
| End point title | Change from Baseline in Dyspnea (EORTC QLQ-C30 Item 8) Score |
|-----------------|--|

End point description:

EORTC QLQ-C30 is a questionnaire to assess the overall QoL of cancer patients. Participant responses to the question: "Were you short of breath?" are scored on a 4-point scale (1=Not at All to 4=Very Much). Using linear transformation, raw scores are standardized, so that scores range from 0 to 100. A lower score indicates a better outcome. Per protocol, the change from baseline in EORTC QLQ-C30 dyspnea (Item 8) score was presented. All randomized participants who received at least one dose of study treatment and have at least one EORTC-QLQ-C30 Item 8 assessment data available.

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

End point timeframe:

Baseline and Week 21

| End point values | Pembrolizumab + Lenvatinib | Pembrolizumab + Placebo | | |
|--|----------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 309 | 308 | | |
| Units: Score on a scale | | | | |
| least squares mean (confidence interval 95%) | -1.35 (-4.75 to 2.04) | -0.47 (-3.94 to 3.00) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Difference in LS Means |
| Comparison groups | Pembrolizumab + Lenvatinib v Pembrolizumab + Placebo |
| Number of subjects included in analysis | 617 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.7088 |
| Method | cLDA model |
| Parameter estimate | Difference in LS means |
| Point estimate | -0.88 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.49 |
| upper limit | 3.74 |

Secondary: Change from Baseline in Cough (EORTC Quality of Life Questionnaire-Lung Cancer Module 13 [QLQ-LC13] Item 31) Score

| | |
|-----------------|--|
| End point title | Change from Baseline in Cough (EORTC Quality of Life Questionnaire-Lung Cancer Module 13 [QLQ-LC13] Item 31) Score |
|-----------------|--|

End point description:

The EORTC QLQ-LC13 is a lung cancer-specific supplemental questionnaire used in combination with the EORTC QLQ-C30. Participant responses to the question "How much did you cough?" are scored on a 4-point scale (1=Not at All to 4=Very Much). Using linear transformation, raw scores are standardized, so that scores range from 0 to 100. A lower score indicates a better outcome. Per protocol, the change from baseline in cough (EORTC QLQ-LC13 Item 31) score was presented. All randomized participants who received at least one dose of study treatment and have at least one EORTC-QLQ-C30 Item 31 assessment data available.

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

End point timeframe:

Baseline and Week 21

| End point values | Pembrolizumab + Lenvatinib | Pembrolizumab + Placebo | | |
|--|----------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 309 | 307 | | |
| Units: Score on a scale | | | | |
| least squares mean (confidence interval 95%) | -9.53 (-12.94 to -6.13) | -5.04 (-8.51 to -1.57) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Difference in LS Means |
| Comparison groups | Pembrolizumab + Lenvatinib v Pembrolizumab + Placebo |
| Number of subjects included in analysis | 616 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0461 ^[1] |
| Method | cLDA model |
| Parameter estimate | Difference in LS means |
| Point estimate | -4.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.91 |
| upper limit | -0.08 |

Notes:

[1] - Two-sided p-value based on cLDA model with covariates for treatment by study visit interaction; stratified by ECOG, region & baseline PDL-1.

Secondary: Change from Baseline in Chest Pain (EORTC QLQ-LC13 Item 40) Score

| | |
|-----------------|---|
| End point title | Change from Baseline in Chest Pain (EORTC QLQ-LC13 Item 40) Score |
|-----------------|---|

End point description:

The EORTC QLQ-LC13 is a lung cancer-specific supplemental questionnaire used in combination with the EORTC QLQ-C30. Participant responses to the question "Have you had pain in your chest?" are scored on a 4-point scale (1=Not at All to 4=Very Much). Using linear transformation, raw scores are standardized, so that scores range from 0 to 100. A lower score indicates a better outcome. Per protocol, the change from baseline in EORTC QLQ-LC13 chest pain (Item 40) score was presented. All randomized participants who received at least one dose of study treatment and have at least one EORTC-QLQ-C30 Item 40 assessment data available.

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

End point timeframe:

Baseline and Week 21

| End point values | Pembrolizumab + Lenvatinib | Pembrolizumab + Placebo | | |
|--|----------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 309 | 307 | | |
| Units: Score on a scale | | | | |
| least squares mean (confidence interval 95%) | -4.64 (-7.45 to -1.84) | -3.55 (-6.42 to -0.68) | | |

Statistical analyses

| Statistical analysis title | Difference in LS Means |
|---|--|
| Comparison groups | Pembrolizumab + Lenvatinib v Pembrolizumab + Placebo |
| Number of subjects included in analysis | 616 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.5596 |
| Method | cLDA model |
| Parameter estimate | Difference in LS means |
| Point estimate | -1.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.78 |
| upper limit | 2.59 |

Secondary: Change from Baseline in Physical Functioning (EORTC QLQ-C30 Items 1-5) Score

| | |
|-----------------|---|
| End point title | Change from Baseline in Physical Functioning (EORTC QLQ-C30 |
|-----------------|---|

End point description:

EORTC QLQ-C30 is a questionnaire to assess the overall QoL of cancer patients. Participant responses to 5 questions about their physical functioning (Items 1 to 5) are scored on a 4-point scale (1=Not at All to 4=Very Much). The combined score of items 1 to 5 was computed by averaging the raw scores of the 5 items and then applying a linear transformation to standardize the average score, so that the combined scores range from 0-100. A higher score indicates a better outcome. Per protocol, the change from baseline in EORTC QLQ-C30 physical functioning (Items 1-5) combined score was presented. All randomized participants who received at least one dose of study treatment and have at least one EORTC-QLQ-C30 Items 1-5 assessment data available.

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

End point timeframe:

Baseline and Week 21

| End point values | Pembrolizumab + Lenvatinib | Pembrolizumab + Placebo | | |
|--|----------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 309 | 308 | | |
| Units: Score on a scale | | | | |
| least squares mean (confidence interval 95%) | -6.73 (-9.35 to -4.10) | -3.72 (-6.40 to -1.04) | | |

Statistical analyses

| Statistical analysis title | Difference in LS Means |
|---|--|
| Comparison groups | Pembrolizumab + Lenvatinib v Pembrolizumab + Placebo |
| Number of subjects included in analysis | 617 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.1116 |
| Method | cLDA model |
| Parameter estimate | Difference in LS means |
| Point estimate | -3.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.71 |
| upper limit | 0.7 |

Secondary: Time to True Deterioration (TTD) in EORTC QLQ-LC13 Chest Pain (Item 40) Scale Score

| | |
|-----------------|---|
| End point title | Time to True Deterioration (TTD) in EORTC QLQ-LC13 Chest Pain (Item 40) Scale Score |
|-----------------|---|

End point description:

EORTC QLQ-LC13 is a lung cancer specific questionnaire. Participant responses to the question: "Have you had pain in your chest?" are scored on a 4-point scale (1=Not at All to 4=Very Much). Using linear transformation, raw scores are standardized, so that scores range from 0-100. A lower score indicates a better outcome. TTD was defined as the time from baseline to first onset of ≥ 10 -point negative change

(decrease) from baseline in cough (Item 40). A longer TTD indicates a better outcome. A value of 9999 indicates that no data were calculated. All randomized participants who received at least one dose of study treatment and have at least one EORTC-QLQ-LC13 Item 40 assessment data available.

| | |
|-------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to approximately 25 months | |

| End point values | Pembrolizumab + Lenvatinib | Pembrolizumab + Placebo | | |
|----------------------------------|----------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 304 | 294 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 9999 (9999 to 9999) | 9999 (9999 to 9999) | | |

Statistical analyses

| Statistical analysis title | Hazard Ratio |
|---|--|
| Comparison groups | Pembrolizumab + Lenvatinib v Pembrolizumab + Placebo |
| Number of subjects included in analysis | 598 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.7457 |
| Method | Stratified Log Rank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.73 |
| upper limit | 1.56 |

Secondary: Time to True Deterioration (TTD) in EORTC QLQ-LC13 Cough (Item 31) Scale Score

| | |
|--|--|
| End point title | Time to True Deterioration (TTD) in EORTC QLQ-LC13 Cough (Item 31) Scale Score |
| End point description: | |
| EORTC QLQ-LC13 is a lung cancer specific questionnaire. Participant responses to the question: "How much did you cough?" are scored on a 4-point scale (1=Not at All to 4=Very Much). Using linear transformation, raw scores are standardized, so that scores range from 0-100. A lower score indicates a better outcome. TTD was defined as the time from baseline to first onset of ≥ 10 -point negative change (decrease) from baseline in cough (Item 31). A longer TTD indicates a better outcome. A value of 9999 indicates that no data were calculated. All randomized participants who received at least one dose of study treatment and have at least one EORTC-QLQ-LC13 Item assessment data available. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to approximately 25 months | |

| End point values | Pembrolizumab + Lenvatinib | Pembrolizumab + Placebo | | |
|----------------------------------|----------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 304 | 294 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 9999 (9999 to 9999) | 9999 (9999 to 9999) | | |

Statistical analyses

| Statistical analysis title | Hazard Ratio |
|---|--|
| Comparison groups | Pembrolizumab + Lenvatinib v Pembrolizumab + Placebo |
| Number of subjects included in analysis | 598 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0079 |
| Method | Stratified Log Rank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.61 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.42 |
| upper limit | 0.88 |

Secondary: Time to True Deterioration (TTD) in EORTC QLQ-C30 Combined Global Health Status /Quality of Life (Items 29 & 30) Scale Combined Score

| | |
|---|---|
| End point title | Time to True Deterioration (TTD) in EORTC QLQ-C30 Combined Global Health Status /Quality of Life (Items 29 & 30) Scale Combined Score |
| End point description: | |
| EORTC QLQ-C30 is a questionnaire to assess QoL of cancer patients. Participant responses to questions on GHS ("How would you rate your overall health during the past week?") and QoL ("How would you rate your overall QoL during the past week?") were scored on a 7-point scale (1= Very poor to 7=Excellent). The combined score of GHS (Item 29) and QoL (Item 30) was computed by averaging raw scores of the 2 items and applying a linear transformation to standardize the average score, so that the combined scores range from 0-100. A higher score indicates a better outcome. TTD was defined as the time from baseline to first onset of ≥10-point negative change (decrease) from baseline in GHS-QoL combined score. A longer TTD indicates a better outcome. A value of 9999 indicates that no data were calculated. All randomized participants who received at least one dose of study treatment and have at least one EORTC-QLQ-C30 Item 29 and Item 30 assessment data available. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to approximately 25 months | |

| End point values | Pembrolizumab + Lenvatinib | Pembrolizumab + Placebo | | |
|----------------------------------|----------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 304 | 297 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 9999 (14.1 to 9999) | 9999 (19.3 to 9999) | | |

Statistical analyses

| Statistical analysis title | Hazard Ratio |
|---|--|
| Comparison groups | Pembrolizumab + Lenvatinib v Pembrolizumab + Placebo |
| Number of subjects included in analysis | 601 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.9601 |
| Method | Stratified Log Rank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.75 |
| upper limit | 1.33 |

Secondary: Time to True Deterioration (TTD) Based on Change from Baseline in the Composite Endpoint of Cough (EORTC QLQ-LC13 Item 31), Chest Pain (EORTC QLQ-LC13 Item 40), or Dyspnea (EORTC QLQ-C30 Item 8)

| | |
|-----------------|--|
| End point title | Time to True Deterioration (TTD) Based on Change from Baseline in the Composite Endpoint of Cough (EORTC QLQ-LC13 Item 31), Chest Pain (EORTC QLQ-LC13 Item 40), or Dyspnea (EORTC QLQ-C30 Item 8) |
|-----------------|--|

End point description:

The EORTC QLQ-C30 is a 30-item questionnaire developed to assess QoL of cancer patients, including a single-item scale score for dyspnea (Item 8; score range: 1=Not at All to 4=Very Much). Used in combination with QLQ-C30, the EORTC QLQ-LC13 is a supplemental lung cancer-specific module, including a single-item scale score for cough (Item 31; score range: 1=Not at All to 4=Very Much) and chest pain (Item 40, score range: 1=Not at All to 4=Very Much). The combined score was computed by averaging raw scores of all items; then applying a linear transformation to standardize average score. Combined scores range from 0-100. A higher score indicates a better outcome. TTD in the composite endpoint (Items 31, 40, & 8) scale score was presented, defined as time to first onset of a ≥ 10 point. 9999 value indicates that no data were calculated. All randomized participants who received at least 1 dose of study treatment & have at least one EORTC-QLQ-C30 or QLQ-LC13 assessment data available.

| | |
|-------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to approximately 25 months | |

| End point values | Pembrolizumab + Lenvatinib | Pembrolizumab + Placebo | | |
|----------------------------------|----------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 49 | 55 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 5.78 (2.79 to 9999) | 9999 (3.45 to 9999) | | |

Statistical analyses

| Statistical analysis title | Hazard Ratio |
|---|--|
| Comparison groups | Pembrolizumab + Lenvatinib v Pembrolizumab + Placebo |
| Number of subjects included in analysis | 104 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.4068 |
| Method | Stratified Log Rank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.31 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.7 |
| upper limit | 2.46 |

Secondary: Time to True Deterioration (TTD) in EORTC QLQ-C30 Dyspnea (Item 8) Scale Score

| | |
|-----------------|--|
| End point title | Time to True Deterioration (TTD) in EORTC QLQ-C30 Dyspnea (Item 8) Scale Score |
|-----------------|--|

End point description:

EORTC QLQ-C30 is a questionnaire to assess the overall QoL of cancer patients. Participant responses to the question: "Were you short of breath?" are scored on a 4-point scale (1=Not at All to 4=Very Much). Using linear transformation, raw scores are standardized, so that scores range from 0 to 100. A lower score indicates a better outcome. TTD was defined as the time from baseline to first onset of ≥ 10 -point negative change (decrease) from baseline in dyspnea (Item 8). A longer TTD indicates a better outcome. A value of 9999 indicates that no data were calculated. All randomized participants who received at least one dose of study treatment and have at least one EORTC-QLQ Item 8 assessment data available.

| | |
|-------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to approximately 25 months | |

| End point values | Pembrolizumab + Lenvatinib | Pembrolizumab + Placebo | | |
|---|----------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 304 | 297 | | |
| Units: Months | | | | |
| arithmetic mean (confidence interval 95%) | 9999 (9999 to 9999) | 9999 (20.8 to 9999) | | |

Statistical analyses

| Statistical analysis title | Hazard Ratio |
|---|--|
| Comparison groups | Pembrolizumab + Lenvatinib v Pembrolizumab + Placebo |
| Number of subjects included in analysis | 601 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.8122 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.75 |
| upper limit | 1.44 |

Secondary: Time to True Deterioration (TTD) Based on Change from Baseline in EORTC QLQ-C30 Physical Functioning (Items 1-5) Score

| | |
|-----------------|--|
| End point title | Time to True Deterioration (TTD) Based on Change from Baseline in EORTC QLQ-C30 Physical Functioning (Items 1-5) Score |
|-----------------|--|

End point description:

EORTC QLQ-C30 is a questionnaire to assess the overall QoL of cancer patients. Participant responses to 5 questions about their physical functioning (Items 1 to 5) are scored on a 4-point scale (1=Not at All to 4=Very Much). The combined score of items 1 to 5 was computed by averaging the raw scores of the 5 items and then applying a linear transformation to standardize the average score, so that the combined scores range from 0-100. A higher score indicates a better outcome. TTD was defined as the time from baseline to first onset of ≥ 10 -point negative change (decrease) from baseline in physical functioning (Items 1 to 5). A longer TTD indicates a better outcome. A value of 9999 indicates that no data were calculated. All randomized participants who received at least one dose of study treatment and have at least one EORTC-QLQ-C30 Items 1-5 assessment data available.

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

End point timeframe:

Up to approximately 25 months

| End point values | Pembrolizumab + Lenvatinib | Pembrolizumab + Placebo | | |
|----------------------------------|-------------------------------|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 304 | 297 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 18.8 (14.1 to 9999) | 9999 (20.0 to 9999) | | |

Statistical analyses

| Statistical analysis title | Hazard Ratio |
|---|--|
| Comparison groups | Pembrolizumab + Lenvatinib v Pembrolizumab + Placebo |
| Number of subjects included in analysis | 601 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.148 |
| Method | Stratified Log Rank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.24 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.92 |
| upper limit | 1.67 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 61 months

Adverse event reporting additional description:

All-cause mortality includes all randomized participants (n=623). Adverse events (AEs) include all randomized participants who received ≥ 1 dose of study drug. Cancer disease progression was not an AE unless study related. MedDRA terms neoplasm progression, malignant neoplasm progression & disease progression unrelated to study drug were excluded.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 26.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------------------|
| Reporting group title | Placebo + Pembrolizumab |
|-----------------------|-------------------------|

Reporting group description: -

| | |
|-----------------------|----------------------------|
| Reporting group title | Lenvatinib + Pembrolizumab |
|-----------------------|----------------------------|

Reporting group description: -

| Serious adverse events | Placebo + Pembrolizumab | Lenvatinib + Pembrolizumab | |
|---|----------------------------|-------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 118 / 312 (37.82%) | 192 / 309 (62.14%) | |
| number of deaths (all causes) | 232 | 229 | |
| number of deaths resulting from adverse events | 23 | 60 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Bladder cancer | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cancer pain | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colorectal adenoma | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Keratoacanthoma | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostate cancer | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin angiosarcoma | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour haemorrhage | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 2 / 309 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Tumour necrosis | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Thrombosis | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Accelerated hypertension | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Embolism | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Embolism arterial | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 312 (0.64%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 2 / 309 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive emergency | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 2 / 309 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral artery stenosis | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral ischaemia | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shock | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Venous thrombosis limb | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vasculitis | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 2 / 312 (0.64%) | 5 / 309 (1.62%) | |
| occurrences causally related to treatment / all | 1 / 2 | 4 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 2 / 309 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 2 / 309 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Axillary pain | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Asthenia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 312 (0.00%) | 5 / 309 (1.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malaise | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 2 / 309 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Polyserositis | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Strangulated hernia | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden death | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 13 / 309 (4.21%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 13 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 13 | |
| Reproductive system and breast disorders | | | |
| Prostatomegaly | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Asthma | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atelectasis | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchial fistula | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Bronchospasm | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 6 / 312 (1.92%) | 2 / 309 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic respiratory disease | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 3 / 312 (0.96%) | 2 / 309 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoptysis | | | |
| subjects affected / exposed | 2 / 312 (0.64%) | 9 / 309 (2.91%) | |
| occurrences causally related to treatment / all | 0 / 2 | 7 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 4 / 6 | |
| Immune-mediated lung disease | | | |
| subjects affected / exposed | 5 / 312 (1.60%) | 4 / 309 (1.29%) | |
| occurrences causally related to treatment / all | 5 / 5 | 4 / 4 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Oesophagobronchial fistula | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pharyngeal inflammation | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 6 / 312 (1.92%) | 2 / 309 (0.65%) | |
| occurrences causally related to treatment / all | 1 / 7 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 3 / 312 (0.96%) | 7 / 309 (2.27%) | |
| occurrences causally related to treatment / all | 3 / 3 | 7 / 7 | |
| deaths causally related to treatment / all | 1 / 1 | 2 / 2 | |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 7 / 309 (2.27%) | |
| occurrences causally related to treatment / all | 0 / 1 | 3 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 4 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 8 / 312 (2.56%) | 7 / 309 (2.27%) | |
| occurrences causally related to treatment / all | 2 / 8 | 5 / 7 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 3 / 309 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 1 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 2 / 2 | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Respiratory distress | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Respiratory failure | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 312 (0.32%) | 4 / 309 (1.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Organising pneumonia | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 2 / 309 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Delirium | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 3 / 309 (0.97%) | |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Amylase increased | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 2 / 309 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 3 / 309 (0.97%) | |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Blood bilirubin increased | | | |
| subjects affected / exposed | 2 / 312 (0.64%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coagulation time prolonged | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Electrocardiogram ST segment elevation | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lipase increased | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Acetabulum fracture | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Compression fracture | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Femur fracture | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intentional overdose | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural complication | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Spinal fracture | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper limb fracture | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| Tracheo-oesophageal fistula | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 2 / 309 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 1 / 2 | |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial flutter | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 2 / 309 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Arteriosclerosis coronary artery | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiac tamponade | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiac ventricular thrombosis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure acute | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 3 / 312 (0.96%) | 3 / 309 (0.97%) | |
| occurrences causally related to treatment / all | 1 / 3 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericardial effusion | | | |
| subjects affected / exposed | 3 / 312 (0.96%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocarditis | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 3 / 309 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Immune-mediated myocarditis | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Nervous system disorders | | | |
| Cerebral haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Altered state of consciousness | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral infarction | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 3 / 309 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Demyelination | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhagic stroke | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Hypersomnia | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic stroke | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Loss of consciousness | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorder | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Posterior reversible encephalopathy syndrome | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 2 / 309 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Presyncope | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal cord compression | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 4 / 312 (1.28%) | 2 / 309 (0.65%) | |
| occurrences causally related to treatment / all | 3 / 4 | 1 / 2 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 2 / 309 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Diarrhoea haemorrhagic | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 8 / 309 (2.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 7 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis ulcerative | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 2 / 309 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 4 / 309 (1.29%) | |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ascites | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal fistula | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal wall haematoma | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysphagia | | | |
| subjects affected / exposed | 2 / 312 (0.64%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric ulcer perforation | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal angiodysplasia | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Ileus | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal pseudo-obstruction | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Intra-abdominal fluid collection | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peptic ulcer | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 4 / 309 (1.29%) | |
| occurrences causally related to treatment / all | 1 / 1 | 5 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oral cavity fistula | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal stenosis | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Melaena | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestinal ulcer | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterocolitis | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 2 / 309 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholangitis | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Portal hypertension | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune-mediated hepatitis | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 2 / 309 (0.65%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis toxic | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 4 / 309 (1.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dermatitis bullous | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dermatosis | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug eruption | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune-mediated dermatitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 2 / 309 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin lesion inflammation | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stevens-Johnson syndrome | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 2 / 309 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subcutaneous emphysema | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vancomycin infusion reaction | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin ulcer | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 3 / 312 (0.96%) | 2 / 309 (0.65%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anuria | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tubulointerstitial nephritis | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract obstruction | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal impairment | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Inappropriate antidiuretic hormone secretion | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypothyroidism | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypophysitis | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperthyroidism | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 2 / 312 (0.64%) | 2 / 309 (0.65%) | |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thyroiditis | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Myalgia | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arthritis | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Connective tissue disorder | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Groin pain | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral disc protrusion | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myositis | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteonecrosis of jaw | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pathological fracture | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rotator cuff syndrome | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Soft tissue mass | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spondyloarthropathy | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neck pain | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Abscess jaw | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis B | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gangrene | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Empyema | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 4 / 312 (1.28%) | 8 / 309 (2.59%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 4 | |
| COVID-19 | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 2 / 309 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningitis aseptic | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 2 / 312 (0.64%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonitis | | | |

| | | | |
|---|------------------|-------------------|--|
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural infection | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumocystis jirovecii pneumonia | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 17 / 312 (5.45%) | 32 / 309 (10.36%) | |
| occurrences causally related to treatment / all | 3 / 19 | 4 / 38 | |
| deaths causally related to treatment / all | 0 / 4 | 0 / 7 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 4 / 309 (1.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 4 / 309 (1.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 2 / 309 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Sepsis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia pseudomonal | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia fungal | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 2 / 309 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung abscess | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 2 / 309 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound infection | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 4 / 309 (1.29%) | |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercalcaemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 312 (0.64%) | 0 / 309 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 2 / 309 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 2 / 312 (0.64%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypophagia | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malnutrition | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 309 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Type 1 diabetes mellitus | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 2 / 309 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Decreased appetite | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 312 (0.00%) | 7 / 309 (2.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Placebo + Pembrolizumab | Lenvatinib + Pembrolizumab | |
|---|----------------------------|-------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 275 / 312 (88.14%) | 296 / 309 (95.79%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 46 / 312 (14.74%) | 122 / 309 (39.48%) | |
| occurrences (all) | 52 | 150 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 32 / 312 (10.26%) | 33 / 309 (10.68%) | |
| occurrences (all) | 41 | 42 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 18 / 312 (5.77%) | 31 / 309 (10.03%) | |
| occurrences (all) | 20 | 42 | |
| Fatigue | | | |
| subjects affected / exposed | 37 / 312 (11.86%) | 44 / 309 (14.24%) | |
| occurrences (all) | 40 | 58 | |
| Chest pain | | | |
| subjects affected / exposed | 15 / 312 (4.81%) | 23 / 309 (7.44%) | |
| occurrences (all) | 15 | 26 | |
| Asthenia | | | |
| subjects affected / exposed | 35 / 312 (11.22%) | 57 / 309 (18.45%) | |
| occurrences (all) | 37 | 86 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 25 / 312 (8.01%) | 29 / 309 (9.39%) | |
| occurrences (all) | 27 | 38 | |
| Dysphonia | | | |

| | | | |
|--|-------------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 4 / 312 (1.28%) 4 | 26 / 309 (8.41%) 29 | |
| Dyspnoea subjects affected / exposed occurrences (all) | 27 / 312 (8.65%) 29 | 34 / 309 (11.00%) 36 | |
| Haemoptysis subjects affected / exposed occurrences (all) | 27 / 312 (8.65%) 49 | 25 / 309 (8.09%) 29 | |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 13 / 312 (4.17%) 13 | 17 / 309 (5.50%) 18 | |
| Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 32 / 312 (10.26%) 42 | 60 / 309 (19.42%) 79 | |
| Amylase increased subjects affected / exposed occurrences (all) | 10 / 312 (3.21%) 11 | 30 / 309 (9.71%) 45 | |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 32 / 312 (10.26%) 49 | 62 / 309 (20.06%) 89 | |
| Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) | 17 / 312 (5.45%) 29 | 35 / 309 (11.33%) 47 | |
| Blood creatinine increased subjects affected / exposed occurrences (all) | 19 / 312 (6.09%) 23 | 23 / 309 (7.44%) 27 | |
| Blood thyroid stimulating hormone increased subjects affected / exposed occurrences (all) | 7 / 312 (2.24%) 11 | 24 / 309 (7.77%) 29 | |
| Lipase increased subjects affected / exposed occurrences (all) | 15 / 312 (4.81%) 18 | 29 / 309 (9.39%) 50 | |
| Platelet count decreased | | | |

| | | | |
|--|-------------------------|---------------------------|--|
| subjects affected / exposed occurrences (all) | 7 / 312 (2.24%) 11 | 32 / 309 (10.36%) 46 | |
| Weight decreased subjects affected / exposed occurrences (all) | 25 / 312 (8.01%) 27 | 83 / 309 (26.86%) 98 | |
| Nervous system disorders | | | |
| Dizziness subjects affected / exposed occurrences (all) | 10 / 312 (3.21%) 11 | 19 / 309 (6.15%) 25 | |
| Headache subjects affected / exposed occurrences (all) | 13 / 312 (4.17%) 13 | 28 / 309 (9.06%) 40 | |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 68 / 312 (21.79%) 88 | 57 / 309 (18.45%) 84 | |
| Gastrointestinal disorders | | | |
| Nausea subjects affected / exposed occurrences (all) | 42 / 312 (13.46%) 76 | 70 / 309 (22.65%) 116 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 39 / 312 (12.50%) 62 | 109 / 309 (35.28%) 208 | |
| Constipation subjects affected / exposed occurrences (all) | 44 / 312 (14.10%) 50 | 37 / 309 (11.97%) 42 | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 13 / 312 (4.17%) 13 | 24 / 309 (7.77%) 27 | |
| Abdominal pain subjects affected / exposed occurrences (all) | 6 / 312 (1.92%) 6 | 27 / 309 (8.74%) 33 | |
| Vomiting subjects affected / exposed occurrences (all) | 17 / 312 (5.45%) 26 | 35 / 309 (11.33%) 56 | |
| Stomatitis | | | |

| | | | |
|--|------------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 12 / 312 (3.85%) 12 | 52 / 309 (16.83%) 71 | |
| Skin and subcutaneous tissue disorders | | | |
| Palmar-plantar erythrodysesthesia syndrome | | | |
| subjects affected / exposed | 3 / 312 (0.96%) | 34 / 309 (11.00%) | |
| occurrences (all) | 3 | 37 | |
| Rash | | | |
| subjects affected / exposed | 33 / 312 (10.58%) | 44 / 309 (14.24%) | |
| occurrences (all) | 37 | 57 | |
| Pruritus | | | |
| subjects affected / exposed | 29 / 312 (9.29%) | 33 / 309 (10.68%) | |
| occurrences (all) | 33 | 44 | |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 17 / 312 (5.45%) | 22 / 309 (7.12%) | |
| occurrences (all) | 25 | 30 | |
| Proteinuria | | | |
| subjects affected / exposed | 36 / 312 (11.54%) | 101 / 309 (32.69%) | |
| occurrences (all) | 55 | 169 | |
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 35 / 312 (11.22%) | 127 / 309 (41.10%) | |
| occurrences (all) | 36 | 171 | |
| Hyperthyroidism | | | |
| subjects affected / exposed | 20 / 312 (6.41%) | 30 / 309 (9.71%) | |
| occurrences (all) | 25 | 35 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 33 / 312 (10.58%) | 39 / 309 (12.62%) | |
| occurrences (all) | 43 | 50 | |
| Back pain | | | |
| subjects affected / exposed | 24 / 312 (7.69%) | 26 / 309 (8.41%) | |
| occurrences (all) | 26 | 28 | |
| Myalgia | | | |
| subjects affected / exposed | 10 / 312 (3.21%) | 17 / 309 (5.50%) | |
| occurrences (all) | 10 | 20 | |

| | | | |
|---|-------------------------|-------------------------|--|
| Pain in extremity subjects affected / exposed occurrences (all) | 14 / 312 (4.49%) 16 | 20 / 309 (6.47%) 23 | |
| Infections and infestations | | | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 19 / 312 (6.09%) 33 | 25 / 309 (8.09%) 39 | |
| Pneumonia subjects affected / exposed occurrences (all) | 14 / 312 (4.49%) 15 | 27 / 309 (8.74%) 28 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 51 / 312 (16.35%) 55 | 77 / 309 (24.92%) 92 | |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 23 / 312 (7.37%) 30 | 25 / 309 (8.09%) 39 | |
| Hypoalbuminaemia subjects affected / exposed occurrences (all) | 20 / 312 (6.41%) 31 | 34 / 309 (11.00%) 39 | |
| Hypocalcaemia subjects affected / exposed occurrences (all) | 11 / 312 (3.53%) 12 | 24 / 309 (7.77%) 31 | |
| Hypokalaemia subjects affected / exposed occurrences (all) | 23 / 312 (7.37%) 28 | 28 / 309 (9.06%) 34 | |
| Hyponatraemia subjects affected / exposed occurrences (all) | 23 / 312 (7.37%) 29 | 37 / 309 (11.97%) 49 | |
| Hyperkalaemia subjects affected / exposed occurrences (all) | 12 / 312 (3.85%) 12 | 17 / 309 (5.50%) 20 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 17 February 2019 | The major changes for amendment 1 (AM 1) were to add clarification for pharmacokinetic blood draws and added that complete urinalysis is required at screening and every 4 cycles. |
| 09 August 2019 | The major changes for AM2 included updates to contraception requirements for males and WOCBP. Male participants must agree to protocol-specific contraception during the intervention period and for at least 30 days after the last dose of lenvatinib/placebo. WOCBP must use a contraceptive method that is highly effective with low user dependency or be abstinent from heterosexual intercourse during the intervention period and for at least 120 days post pembrolizumab or 30 days post lenvatinib/matching placebo, whichever occurs last. |
| 16 January 2020 | The major change for AM3 was to clarify that ECG is only required at EOT and safety follow up visits when lenvatinib/matching placebo is discontinued. |
| 20 April 2021 | The major change for AM5 was to remove collection of pembrolizumab and lenvatinib PK and pembrolizumab ADA sampling. |
| 24 November 2021 | The major change for AM6 included unblinding of the study and removing lenvatinib and matching placebo from the study, stopping collection of ePRO data and to add that the study will remain open to allow ongoing participants to continue treatment with open-label pembrolizumab monotherapy up to a maximum of 35 administrations. |
| 13 December 2022 | The major change for AM7 was to do the entity name change and update the address. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported