



Clinical trial results:

A Phase III Randomized Trial of MK-3475 (Pembrolizumab) versus Standard Treatment in Subjects with Recurrent or Metastatic Head and Neck Cancer

Summary

| | |
|--------------------------|-------------------------------------|
| EudraCT number | 2014-001749-26 |
| Trial protocol | IE LT DE BE PT NL HU IT ES FR PL SE |
| Global end of trial date | |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v2 |
| This version publication date | 18 October 2018 |
| First version publication date | 18 May 2018 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | MK-3475-040 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02252042 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Merck Sharp & Dohme Corp. |
| Sponsor organisation address | 2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033 |
| Public contact | Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com |
| Scientific contact | Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|-------------|
| Analysis stage | Interim |
| Date of interim/final analysis | 15 May 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 15 May 2017 |
| Global end of trial reached? | No |

Notes:

General information about the trial

Main objective of the trial:

This is a study of pembrolizumab (MK-3475) versus standard treatment (methotrexate, docetaxel or cetuximab) for the treatment of recurrent or metastatic head and neck squamous cell cancer (HNSCC). Participants will be randomly assigned to receive either pembrolizumab or Investigator's choice of standard treatment.

The primary study hypothesis is that pembrolizumab treatment prolongs Overall Survival (OS) when compared to standard treatment.

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 | 17 November 2014 |
| 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 | Belgium: 17 |
| Country: Number of subjects enrolled | Canada: 33 |
| Country: Number of subjects enrolled | France: 51 |
| Country: Number of subjects enrolled | Germany: 24 |
| Country: Number of subjects enrolled | Hungary: 19 |
| Country: Number of subjects enrolled | Ireland: 4 |
| Country: Number of subjects enrolled | Italy: 29 |
| Country: Number of subjects enrolled | Korea, Republic of: 22 |
| Country: Number of subjects enrolled | Lithuania: 7 |
| Country: Number of subjects enrolled | Mexico: 6 |
| Country: Number of subjects enrolled | Netherlands: 2 |
| Country: Number of subjects enrolled | Poland: 21 |
| Country: Number of subjects enrolled | Portugal: 30 |
| Country: Number of subjects enrolled | Russian Federation: 30 |
| Country: Number of subjects enrolled | Spain: 26 |
| Country: Number of subjects enrolled | Sweden: 3 |
| Country: Number of subjects enrolled | Switzerland: 18 |

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 54 |
| Country: Number of subjects enrolled | United States: 94 |
| Worldwide total number of subjects | 495 |
| EEA total number of subjects | 287 |

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) | 332 |
| From 65 to 84 years | 162 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This results disclosure is based on a data cutoff date of 15 May 2017, at which time 99 participants were ongoing in the study.

Period 1

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

Arms

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

Arm description:

Participants received pembrolizumab 200 mg intravenous (IV) on Day 1 of each 3-week cycle.

| | |
|--|----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Pembrolizumab |
| Investigational medicinal product code | MK-3475 |
| Other name | KEYTRUDA® |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

200 mg via intravenous (IV) infusion

| | |
|------------------|-------------------|
| Arm title | Active Comparator |
|------------------|-------------------|

Arm description:

Participants received methotrexate 40 mg/m² IV (may have been escalated to 60 mg/m² maximum dose) on Days 1, 8, and 15 of each 3-week cycle; or docetaxel 75 mg/m² IV on Day 1 of each 3-week cycle; or cetuximab 400 mg/m² IV loading dose on Day 1 and 250 mg/m² IV on Days 8 and 15 of Cycle 1, followed by cetuximab 250 mg/m² on Days 1, 8, and 15 of each subsequent 3-week cycle.

| | |
|--|---------------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Methotrexate |
| Investigational medicinal product code | |
| Other name | OTREXUP™ RASUVO® RHEUMATREX® TREXALL™ |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

40 mg/m² IV infusion (may be escalated to 60 mg/m² maximum dose)

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Cetuximab |
| Investigational medicinal product code | |
| Other name | ERBITUX® |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Loading dose: 400 mg/m² via IV infusion

Maintenance dose: 250 mg/m² via IV infusion

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Docetaxel |
| Investigational medicinal product code | |
| Other name | TAXOTERE® |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

75 mg/m² via IV infusion

| Number of subjects in period 1 | Pembrolizumab | Active Comparator |
|---------------------------------------|---------------|-------------------|
| Started | 247 | 248 |
| Treated | 246 | 234 |
| Completed | 0 | 0 |
| Not completed | 247 | 248 |
| Adverse event, serious fatal | 170 | 192 |
| Consent withdrawn by subject | 13 | 20 |
| Physician decision | - | 1 |
| Ongoing in study | 64 | 35 |

Baseline characteristics

Reporting groups

| | |
|--|-------------------|
| Reporting group title | Pembrolizumab |
| Reporting group description: | |
| Participants received pembrolizumab 200 mg intravenous (IV) on Day 1 of each 3-week cycle. | |
| Reporting group title | Active Comparator |
| Reporting group description: | |
| Participants received methotrexate 40 mg/m ² IV (may have been escalated to 60 mg/m ² maximum dose) on Days 1, 8, and 15 of each 3-week cycle; or docetaxel 75 mg/m ² IV on Day 1 of each 3-week cycle; or cetuximab 400 mg/m ² IV loading dose on Day 1 and 250 mg/m ² IV on Days 8 and 15 of Cycle 1, followed by cetuximab 250 mg/m ² on Days 1, 8, and 15 of each subsequent 3-week cycle. | |

| Reporting group values | Pembrolizumab | Active Comparator | Total |
|---|---------------|-------------------|-------|
| Number of subjects | 247 | 248 | 495 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 165 | 167 | 332 |
| From 65-84 years | 81 | 81 | 162 |
| 85 years and over | 1 | 0 | 1 |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 60.3 | 60.2 | |
| standard deviation | ± 9.8 | ± 8.6 | - |
| Sex: Female, Male | | | |
| Units: Subjects | | | |
| Female | 40 | 43 | 83 |
| Male | 207 | 205 | 412 |
| Programmed Cell Death-Ligand 1 (PD-L1) Expression Level: Tumor Proportion Score (TPS) | | | |
| Participants were assessed for their PD-L1 tumor expression level by immunohistochemistry assay using tumor tissue from a newly obtained biopsy. Participants with a TPS ≥50% were classified as PD-L1 strongly positive and participants with a TPS <50% were classified as not strongly positive. | | | |
| Units: Subjects | | | |
| TPS=0% | 103 | 93 | 196 |
| 1%≤TPS<50% | 79 | 87 | 166 |
| TPS ≥50% | 64 | 65 | 129 |
| Missing | 1 | 3 | 4 |
| Race (NIH/OMB) | | | |
| The race of participants is presented. | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 2 | 0 | 2 |
| Asian | 15 | 16 | 31 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 3 | 7 | 10 |
| White | 207 | 207 | 414 |
| More than one race | 4 | 3 | 7 |
| Unknown or Not Reported | 16 | 15 | 31 |
| Eastern Cooperative Oncology Group | | | |

| | | | |
|--|-----|-----|-----|
| (ECOG) Performance Status (PS) | | | |
| Participants were assessed for ECOG PS: Grade 0: Fully active, able to carry on all pre-disease performance without restriction; Grade 1: Restricted in physically strenuous activity but ambulatory & able to carry out work of a light or sedentary nature; Grade 2: Ambulatory & capable of all selfcare but unable to carry out any work activities, up & about more than 50% of waking hours; Grade 3: Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours; Grade 4: Completely disabled, cannot carry on any selfcare, totally confined to bed or chair or Grade 5: Dead. | | | |
| Units: Subjects | | | |
| EGOG PS=0 | 71 | 67 | 138 |
| EGOG PS=1 | 176 | 180 | 356 |
| EGOG PS=2 | 0 | 1 | 1 |
| Human Papillomavirus (HPV) Tumor Status | | | |
| Participants were assessed for the presence or absence of HPV in their tumors. | | | |
| Units: Subjects | | | |
| Positive HPV Status | 61 | 58 | 119 |
| Negative HPV Status | 186 | 190 | 376 |
| PD-L1 Combined Positive Score (CPS) Status | | | |
| Participants were assessed for their PD-L1 tumor expression level by immunohistochemistry assay using tumor tissue from a newly obtained biopsy. Participants with a CPS ≥ 1 were classified as PD-L1 positive and participants with a CPS < 1 were classified as PD-L1 negative. | | | |
| Units: Subjects | | | |
| PD-L1 CPS < 1 | 50 | 54 | 104 |
| PD-L1 CPS ≥ 1 | 196 | 191 | 387 |
| Missing | 1 | 3 | 4 |

End points

End points reporting groups

| | |
|--|--|
| Reporting group title | Pembrolizumab |
| Reporting group description: | |
| Participants received pembrolizumab 200 mg intravenous (IV) on Day 1 of each 3-week cycle. | |
| Reporting group title | Active Comparator |
| Reporting group description: | |
| Participants received methotrexate 40 mg/m ² IV (may have been escalated to 60 mg/m ² maximum dose) on Days 1, 8, and 15 of each 3-week cycle; or docetaxel 75 mg/m ² IV on Day 1 of each 3-week cycle; or cetuximab 400 mg/m ² IV loading dose on Day 1 and 250 mg/m ² IV on Days 8 and 15 of Cycle 1, followed by cetuximab 250 mg/m ² on Days 1, 8, and 15 of each subsequent 3-week cycle. | |
| Subject analysis set title | Pembrolizumab with PD-L1 ≥ 1% CPS |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| All randomized participants who received Pembrolizumab and had PD-L1 ≥ 1% CPS. Participants are included in the treatment arm to which they were randomized. | |
| Subject analysis set title | Active Comparator with PD-L1 ≥ 1% CPS |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| All randomized participants with PD-L1 ≥ 1% CPS who received Active Comparator. Participants are included in the treatment group to which they were randomized. | |
| Subject analysis set title | Pembrolizumab with CR or PR |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| All randomized participants who received Pembrolizumab and demonstrated a Complete Response (CR) or Partial Response (PR) according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). Participants are included in the treatment arm to which they were randomized. | |
| Subject analysis set title | Active Comparator with CR or PR |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| All randomized participants who received Active Comparator and demonstrated a CR or PR according to RECIST 1.1. Participants are included in the treatment arm to which they were randomized. | |
| Subject analysis set title | Pembrolizumab with PD-L1 ≥ 1% CPS and CR or PR |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| All randomized participants who received Pembrolizumab, had PD-L1 ≥ 1% CPS and experienced a CR or PR. Participants are included in the treatment arm to which they were randomized. | |
| Subject analysis set title | Active Comparator with PD-L1 ≥ 1% CPS and CR or PR |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| All randomized participants who received Active Comparator, had PD-L1 ≥ 1% CPS and experienced a CR or PR. Participants are included in the treatment arm to which they were randomized. | |

Primary: Initial Overall Survival (OS) for All Participants

| | |
|--|--|
| End point title | Initial Overall Survival (OS) for All Participants |
| End point description: | |
| OS was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the final analysis were to be censored at the date of the last follow-up. The OS for all participants is presented. These initial OS results are based on a data cutoff date of 15-May-2017 with a database lock date of 04-Jun-2017. At the time of the database lock of 04-Jun-2017, there was incomplete collection of survival data for 12 participants. The efficacy population consisted of all randomized participants. Participants are included in the treatment group to which they were randomized. | |
| End point type | Primary |

End point timeframe:

Up to approximately 2 years (Database lock on 04-Jun-2017)

| End point values | Pembrolizumab | Active Comparator | | |
|----------------------------------|------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 247 | 248 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 8.5 (6.4 to 9.5) | 7.1 (5.9 to 8.1) | | |

Statistical analyses

| Statistical analysis title | Hazard Ratio |
|--|-----------------------------------|
| Statistical analysis description: | |
| Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs. 1), HPV status (Positive vs. Negative) & PD-L1 status (Strongly Positive, Not Strongly Positive) | |
| Comparison groups | Pembrolizumab v Active Comparator |
| Number of subjects included in analysis | 495 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0316 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.82 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.67 |
| upper limit | 1.01 |

Primary: Updated Final OS for All Participants

| End point title | Updated Final OS for All Participants |
|---|---------------------------------------|
| End point description: | |
| OS was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the final analysis were to be censored at the date of the last follow-up. The updated OS for all participants is presented. These OS results are after complete acquisition of all outstanding survival data using a 15-May-2017 data cutoff date with a database update date of 13-Oct-2017. The efficacy population consisted of all randomized participants. Participants are included in the treatment group to which they were randomized. | |
| End point type | Primary |
| End point timeframe: | |
| Up to approximately 2 years (Database update on 13-Oct-2017) | |

| End point values | Pembrolizumab | Active Comparator | | |
|----------------------------------|------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 247 | 248 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 8.4 (6.4 to 9.4) | 6.9 (5.9 to 8.0) | | |

Statistical analyses

| Statistical analysis title | Hazard Ratio |
|---|-----------------------------------|
| Statistical analysis description: | |
| Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs. 1), HPV status (Positive vs. Negative) & PD-L1 status (Strongly Positive, Not Strongly Positive). Pembrolizumab is the numerator; Active Comparator is the denominator. | |
| Comparison groups | Pembrolizumab v Active Comparator |
| Number of subjects included in analysis | 495 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.01605 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.65 |
| upper limit | 0.98 |

Secondary: OS for Participants With PD-L1-Positive Expression Defined by $\geq 1\%$ CPS (PD-L1 $\geq 1\%$ CPS)

| | |
|---|---|
| End point title | OS for Participants With PD-L1-Positive Expression Defined by $\geq 1\%$ CPS (PD-L1 $\geq 1\%$ CPS) |
| End point description: | |
| OS was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the final analysis will be censored at the date of the last follow-up. The OS for all participants with PD-L1 expression $\geq 1\%$ CPS is presented. These efficacy results are after complete acquisition of all outstanding survival data using a 15-May-2017 data cutoff date with a database update date of 13-Oct-2017. The efficacy population consisted of all randomized participants with PD-L1 $\geq 1\%$ CPS. Participants are included in the treatment group to which they were randomized. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to approximately 2 years | |

| End point values | Pembrolizumab with PD-L1 \geq 1% CPS | Active Comparator with PD-L1 \geq 1% CPS | | |
|----------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 196 | 191 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 8.7 (6.9 to 11.4) | 7.1 (5.7 to 8.3) | | |

Statistical analyses

| Statistical analysis title | OS Hazard Ratio, CPS \geq 1% CPS |
|---|---|
| Statistical analysis description: | |
| Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs. 1), HPV status (Positive vs. Negative) & PD-L1 status (Strongly Positive, Not Strongly Positive). Pembrolizumab is the numerator; Active Comparator is the denominator. | |
| Comparison groups | Pembrolizumab with PD-L1 \geq 1% CPS v Active Comparator with PD-L1 \geq 1% CPS |
| Number of subjects included in analysis | 387 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.00493 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.74 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.58 |
| upper limit | 0.93 |

Secondary: Progression-free Survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 for All Participants

| | |
|---|--|
| End point title | Progression-free Survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 for All Participants |
| End point description: | |
| PFS was defined as the time from randomization to the first documented progressive disease (PD) per RECIST 1.1 based on blinded central imaging vendor review or death due to any cause, whichever occurred first. Per RECIST 1.1, PD was defined as at least a 20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also have demonstrated an absolute increase of at least 5 mm. Note: The appearance of one or more new lesions was also considered PD. The PFS per RECIST 1.1 for all participants is presented. These efficacy results are after complete acquisition of all outstanding survival data using a 15-May-2017 data cutoff date with a database update date of 13-Oct-2017. The efficacy population consisted of all randomized participants. Participants are included in the treatment group to which they were randomized. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to approximately 2 years | |

| End point values | Pembrolizumab | Active Comparator | | |
|----------------------------------|------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 247 | 248 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 2.1 (2.1 to 2.3) | 2.3 (2.1 to 2.8) | | |

Statistical analyses

| Statistical analysis title | Hazard Ratio |
|---|-----------------------------------|
| Statistical analysis description: | |
| Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs. 1), HPV status (Positive vs. Negative) & PD-L1 status (Strongly Positive, Not Strongly Positive). Pembrolizumab is the numerator; Active Comparator is the denominator. | |
| Comparison groups | Pembrolizumab v Active Comparator |
| Number of subjects included in analysis | 495 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.32504 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.96 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.79 |
| upper limit | 1.16 |

Secondary: PFS per RECIST 1.1 in Participants With PD-L1 ≥1% CPS

| | |
|--|---|
| End point title | PFS per RECIST 1.1 in Participants With PD-L1 ≥1% CPS |
| End point description: | |
| PFS was defined as the time from randomization to the first documented PD per RECIST 1.1 based on blinded central imaging vendor review or death due to any cause, whichever occurred first. Per RECIST 1.1, PD was defined as at least a 20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also have demonstrated an absolute increase of at least 5 mm. Note: The appearance of one or more new lesions was also considered PD. The PFS per RECIST 1.1 for all participants with PD-L1 expression ≥1% CPS is presented. These efficacy results are after complete acquisition of all outstanding survival data using a 15-May-2017 data cutoff date with a database update date of 13-Oct-2017. The efficacy population consisted of all randomized participants with PD-L1 ≥1% CPS. Participants are included in the treatment group to which they were randomized. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to approximately 2 years | |

| End point values | Pembrolizumab with PD-L1 \geq 1% CPS | Active Comparator with PD-L1 \geq 1% CPS | | |
|----------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 196 | 191 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 2.2 (2.1 to 3.0) | 2.3 (2.1 to 3.0) | | |

Statistical analyses

| Statistical analysis title | Hazard Ratio |
|---|---|
| Statistical analysis description: Cox regression model with treatment as a single covariate. Pembrolizumab is the numerator; Active Comparator is the denominator. | |
| Comparison groups | Pembrolizumab with PD-L1 \geq 1% CPS v Active Comparator with PD-L1 \geq 1% CPS |
| Number of subjects included in analysis | 387 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.07736 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.86 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.69 |
| upper limit | 1.06 |

Secondary: Objective Response Rate (ORR) per RECIST 1.1 in All Participants

| End point title | Objective Response Rate (ORR) per RECIST 1.1 in All Participants |
|--|--|
| End point description: ORR was defined as the percentage of the participants in the analysis population who had 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 based on blinded central imaging vendor review with or without confirmation. The ORR per RECIST 1.1 for all participants is presented. These efficacy results are after complete acquisition of all outstanding survival data using a 15-May-2017 data cutoff date with a database update date of 13-Oct-2017. The efficacy population consisted of all randomized participants. Participants are included in the treatment group to which they were randomized. | |
| End point type | Secondary |
| End point timeframe: Up to approximately 2 years | |

| End point values | Pembrolizumab | Active Comparator | | |
|-----------------------------------|---------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 247 | 248 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 14.6 (10.4 to 19.6) | 10.1 (6.6 to 14.5) | | |

Statistical analyses

| Statistical analysis title | Difference in Percentages |
|--|-----------------------------------|
| Statistical analysis description: | |
| Stratified by ECOG PS (0 vs. 1), HPV status (Positive vs. Negative) & PD-L1 status (Strongly Positive, Not Strongly Positive). H0: difference in % = 0; H1: difference in % > 0. | |
| Comparison groups | Pembrolizumab v Active Comparator |
| Number of subjects included in analysis | 495 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.061 |
| Method | Logrank |
| Parameter estimate | Difference in percentages |
| Point estimate | 4.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.2 |
| upper limit | 10.6 |

Secondary: ORR per RECIST 1.1 in Participants With PD-L1 ≥1% CPS

| End point title | ORR per RECIST 1.1 in Participants With PD-L1 ≥1% CPS |
|---|---|
| End point description: | |
| ORR was defined as the percentage of the participants in the analysis population who had a CR (Disappearance of all target lesions) or a PR (At least a 30% decrease in the sum of diameters of target lesions per RECIST 1.1 based on blinded central imaging vendor review with or without confirmation. The ORR per RECIST 1.1 for all participants with PD-L1 expression ≥1% CPS is presented. These efficacy results are after complete acquisition of all outstanding survival data using a 15-May-2017 data cutoff date with a database update date of 13-Oct-2017. The efficacy population consisted of all randomized participants with PD-L1 ≥1% CPS. Participants are included in the treatment group to which they were randomized. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to approximately 2 years | |

| End point values | Pembrolizumab with PD-L1 \geq 1% CPS | Active Comparator with PD-L1 \geq 1% CPS | | |
|-----------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 196 | 191 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 17.3 (12.3 to 23.4) | 9.9 (6.1 to 15.1) | | |

Statistical analyses

| Statistical analysis title | Difference in Percentages |
|---|---|
| Statistical analysis description: | |
| Stratified by ECOG PS (0 vs. 1), HPV status (Positive vs. Negative) & PD-L1 status (Strongly Positive, Not Strongly Positive). H0: difference in %=0; H1: difference in %>0 | |
| Comparison groups | Pembrolizumab with PD-L1 \geq 1% CPS v Active Comparator with PD-L1 \geq 1% CPS |
| Number of subjects included in analysis | 387 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0171 |
| Method | Logrank |
| Parameter estimate | Difference in percentages |
| Point estimate | 7.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.6 |
| upper limit | 14.6 |

Secondary: Duration of Response (DOR) per RECIST 1.1 in All Participants

| End point title | Duration of Response (DOR) per RECIST 1.1 in All Participants |
|---|---|
| End point description: | |
| For participants who demonstrated a confirmed CR or PR per RECIST 1.1, DOR was defined as the time from first documented evidence of confirmed CR or PR per RECIST 1.1 until PD per RECIST 1.1 or death due to 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 have demonstrated an absolute increase of \geq 5 mm. DOR assessments were based on blinded central imaging vendor review with confirmation. The DOR per RECIST 1.1 for all participants who experienced a confirmed CR or PR is presented. These efficacy results are after complete acquisition of all outstanding survival data using a 15-May-2017 data cutoff date with a database update date of 13-Oct-2017. The efficacy population consisted of all randomized participants who demonstrated a confirmed CR or PR per RECIST 1.1. Participants are included in the treatment group to which they were randomized. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to approximately 2 years | |

| End point values | Pembrolizumab with CR or PR | Active Comparator with CR or PR | | |
|-------------------------------|-----------------------------|---------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 26 | 18 | | |
| Units: Months | | | | |
| median (full range (min-max)) | 18.4 (2.7 to 18.4) | 5.0 (1.4 to 18.8) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: DOR per RECIST 1.1 in Participants With PD-L1 \geq 1% CPS

| | |
|---|---|
| End point title | DOR per RECIST 1.1 in Participants With PD-L1 \geq 1% CPS |
| End point description: | |
| For participants who demonstrated a confirmed CR or PR per RECIST 1.1, DOR was defined as the time from 1st documented evidence of CR or PR per RECIST 1.1 until PD per RECIST 1.1 or death due to 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, the sum must also have demonstrated an absolute increase of \geq 5 mm. DOR assessments were based on blinded central imaging vendor review with confirmation. The DOR per RECIST 1.1 for all participants with PD-L1 \geq 1% CPS who experienced a confirmed CR or PR is presented. These efficacy results are after complete acquisition of all outstanding survival data using a 15-May-2017 data cutoff date with a database update date of 13-Oct-2017. The efficacy population consisted of all randomized participants with PD-L1 \geq 1% CPS who demonstrated a confirmed CR or PR per RECIST 1.1. Participants are included in the treatment group to which they were randomized. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to approximately 2 years | |

| End point values | Pembrolizumab with PD-L1 \geq 1% CPS and CR or PR | Active Comparator with PD-L1 \geq 1% CPS and CR or PR | | |
|-------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 26 | 15 | | |
| Units: Months | | | | |
| median (full range (min-max)) | 18.4 (2.7 to 18.4) | 9.6 (1.4 to 18.8) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP) per RECIST 1.1 in All Participants

| | |
|---|--|
| End point title | Time to Progression (TTP) per RECIST 1.1 in All Participants |
| End point description: | |
| TTP was defined as the time from randomization to the first documented PD based on assessments by | |

the blinded central imaging vendor review per RECIST 1.1. Per RECIST 1.1, PD was defined as at least a 20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also have demonstrated an absolute increase of at least 5 mm. Note: The appearance of one or more new lesions was also considered PD. The TTP per RECIST 1.1 for all participants is presented. These efficacy results are after complete acquisition of all outstanding survival data using a 15-May-2017 data cutoff date with a database update date of 13-Oct-2017. The efficacy population consisted of all randomized participants. Participants are included in the treatment group to which they were randomized.

| | |
|-----------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to approximately 2 years | |

| End point values | Pembrolizumab | Active Comparator | | |
|----------------------------------|------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 247 | 248 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 2.2 (2.1 to 3.3) | 2.2 (2.1 to 3.4) | | |

Statistical analyses

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

Statistical analysis description:

Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs. 1), HPV status (Positive vs. Negative) & PD-L1 status (Strongly Positive, Not Strongly Positive)

| | |
|---|-----------------------------------|
| Comparison groups | Pembrolizumab v Active Comparator |
| Number of subjects included in analysis | 495 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.14545 ^[1] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.89 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.7 |
| upper limit | 1.12 |

Notes:

[1] - p-value stratified by ECOG PS (0 vs. 1), HPV status (Positive vs. Negative) & PD-L1 status (Strongly Positive, Not Strongly Positive)

Secondary: TTP per RECIST 1.1 in Participants With PD-L1 ≥1% CPS

| | |
|-----------------|---|
| End point title | TTP per RECIST 1.1 in Participants With PD-L1 ≥1% CPS |
|-----------------|---|

End point description:

TTP was defined as the time from randomization to the first documented PD based on assessments by the blinded central imaging vendor review per RECIST 1.1. Per RECIST 1.1, PD was defined as at least a 20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also have demonstrated an absolute increase of at least 5 mm. Note: The appearance of one or more new lesions was also considered PD. The TTP per RECIST 1.1 for all participants with PD-L1

≥1% CPS is presented. These efficacy results are after complete acquisition of all outstanding survival data using a 15-May-2017 data cutoff date with a database update date of 13-Oct-2017. The efficacy population consisted of all randomized participants with PD-L1 ≥1% CPS. Participants are included in the treatment group to which they were randomized.

| | |
|-----------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to approximately 2 years | |

| End point values | Pembrolizumab with PD-L1 ≥1% CPS | Active Comparator with PD-L1 ≥1% CPS | | |
|-------------------------------|----------------------------------|--------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 196 | 191 | | |
| Units: Months | | | | |
| median (full range (min-max)) | 2.7 (2.1 to 3.5) | 2.3 (2.1 to 3.4) | | |

Statistical analyses

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

Statistical analysis description:

Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs. 1), HPV status (Positive vs. Negative) & PD-L1 status (Strongly Positive, Not Strongly Positive).

| | |
|---|---|
| Comparison groups | Pembrolizumab with PD-L1 ≥1% CPS v Active Comparator with PD-L1 ≥1% CPS |
| Number of subjects included in analysis | 387 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.05851 ^[2] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.81 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.62 |
| upper limit | 1.06 |

Notes:

[2] - p-value stratified by ECOG PS (0 vs. 1), HPV status (Positive vs. Negative) & PD-L1 status (Strongly Positive, Not Strongly Positive)

Secondary: PFS per Modified RECIST in All Participants

| | |
|-----------------|---|
| End point title | PFS per Modified RECIST in All Participants |
|-----------------|---|

End point description:

PFS was defined as the time from randomization to the 1st documented PD on per RECIST 1.1 based on blinded central imaging vendor review or death due to any cause, whichever occurred first. Per RECIST 1.1, PD was defined as ≥20% increase in the sum of diameters of target lesions. In addition, the sum must also have demonstrated an absolute increase of ≥5 mm. Modified RECIST is similar to RECIST 1.1 with the exception that confirmation assessment of PD (≥4 weeks after the initial PD assessment) was required for participants who remained on treatment following documented PD per RECIST 1.1. The PFS

per modified RECIST for all participants is presented. These efficacy results are after complete acquisition of all outstanding survival data using a 15-May-2017 data cutoff date with a database update date of 13-Oct-2017. The efficacy population consisted of all randomized participants. Participants are included in the treatment group to which they were randomized.

| | |
|-----------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to approximately 2 years | |

| End point values | Pembrolizumab | Active Comparator | | |
|----------------------------------|------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 247 | 248 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 3.5 (3.1 to 4.4) | 4.8 (4.1 to 5.7) | | |

Statistical analyses

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

Statistical analysis description:

Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs. 1), HPV status (Positive vs. Negative) & PD-L1 status (Strongly Positive, Not Strongly Positive). Pembrolizumab is the numerator; Active Comparator is the denominator.

| | |
|---|-----------------------------------|
| Comparison groups | Pembrolizumab v Active Comparator |
| Number of subjects included in analysis | 495 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.65759 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.86 |
| upper limit | 1.27 |

Secondary: PFS per Modified RECIST 1.1 in Participants With PD-L1 ≥1% CPS

| | |
|-----------------|--|
| End point title | PFS per Modified RECIST 1.1 in Participants With PD-L1 ≥1% CPS |
|-----------------|--|

End point description:

PFS was defined as the time from randomization to the 1st documented PD per RECIST 1.1 based on blinded central imaging vendor review or death, whichever occurred first. Per RECIST 1.1, PD was defined as ≥20% increase in the sum of diameters of target lesions. In addition, the sum must also have demonstrated an absolute increase of ≥5 mm. Modified RECIST is similar to RECIST 1.1 with the exception that a confirmation assessment of PD (≥4 weeks after the initial PD assessment) was required for participants who remained on treatment following a documented PD per RECIST 1.1. The PFS per modified RECIST for all participants with PD-L1 ≥1% CPS is presented. These efficacy results are after complete acquisition of all outstanding survival data using a 15-May-2017 data cutoff date with a

database update date of 13-Oct-2017. The efficacy population consisted of all randomized participants with PD-L1 $\geq 1\%$ CPS. Participants are included in the treatment group to which they were randomized.

| | |
|-----------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to approximately 2 years | |

| End point values | Pembrolizumab with PD-L1 $\geq 1\%$ CPS | Active Comparator with PD-L1 $\geq 1\%$ CPS | | |
|----------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 196 | 191 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 3.6 (3.1 to 4.6) | 4.8 (4.1 to 5.7) | | |

Statistical analyses

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

Statistical analysis description:

Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs. 1), HPV status (Positive vs. Negative) & PD-L1 status (Strongly Positive, Not Strongly. Pembrolizumab is the numerator; Active Comparator is the denominator. Positive).

| | |
|---|---|
| Comparison groups | Pembrolizumab with PD-L1 $\geq 1\%$ CPS v Active Comparator with PD-L1 $\geq 1\%$ CPS |
| Number of subjects included in analysis | 387 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.51982 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.81 |
| upper limit | 1.26 |

Secondary: Number of Participants Who Experienced At Least One Adverse Event (AE) in All Participants

| | |
|-----------------|--|
| End point title | Number of Participants Who Experienced At Least One Adverse Event (AE) in All Participants |
|-----------------|--|

End point description:

An AE was defined as any untoward medical occurrence in a participant administered a study treatment and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the study treatment or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse

change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of study treatment, is also an AE. The number of all participants who experienced at least one AE is presented. The safety population consisted of all randomized participants who received at least one dose of study treatment.

| | |
|-------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to approximately 27 months | |

| End point values | Pembrolizumab | Active Comparator | | |
|-----------------------------|-----------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 246 | 234 | | |
| Units: Participants | 238 | 227 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Experienced At Least One AE in Participants With PD-L1 $\geq 1\%$ CPS

| | |
|-----------------|--|
| End point title | Number of Participants Who Experienced At Least One AE in Participants With PD-L1 $\geq 1\%$ CPS |
|-----------------|--|

End point description:

An AE was defined as any untoward medical occurrence in a participant administered a study treatment and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the study treatment or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of study treatment, is also an AE. The number of all participants with PD-L1 $\geq 1\%$ CPS who experienced at least one AE is presented. The safety population consisted of all randomized participants with PD-L1 $\geq 1\%$ CPS who received at least one dose of study treatment.

| | |
|-------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to approximately 27 months | |

| End point values | Pembrolizumab with PD-L1 $\geq 1\%$ CPS | Active Comparator with PD-L1 $\geq 1\%$ CPS | | |
|-----------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 195 | 183 | | |
| Units: Participants | 192 | 178 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Discontinued Study Treatment Due to an AE in All Participants

| | |
|-----------------|--|
| End point title | Number of Participants Who Discontinued Study Treatment Due to an AE in All Participants |
|-----------------|--|

End point description:

The number of all participants who discontinued study treatment due to an AE is presented. The safety population consisted of all randomized participants who received at least one dose of study treatment.

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

End point timeframe:

Up to approximately 2 years

| End point values | Pembrolizumab | Active Comparator | | |
|-----------------------------|-----------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 246 | 234 | | |
| Units: Participants | 28 | 37 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Discontinued Study Treatment Due to an AE in Participants With PD-L1 \geq 1% CPS

| | |
|-----------------|---|
| End point title | Number of Participants Who Discontinued Study Treatment Due to an AE in Participants With PD-L1 \geq 1% CPS |
|-----------------|---|

End point description:

The number of all participants with PD-L1 \geq 1% CPS who discontinued study treatment due to an AE is presented. The safety population consisted of all randomized participants with PD-L1 \geq 1% CPS who received at least one dose of study treatment.

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

End point timeframe:

Up to approximately 2 years

| End point values | Pembrolizumab with PD-L1 \geq 1% CPS | Active Comparator with PD-L1 \geq 1% CPS | | |
|-----------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 195 | 183 | | |
| Units: Participants | 24 | 30 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 27 months (Up to 90 days after last dose of study drug)

Adverse event reporting additional description:

Participants with ≥ 1 dose of study drug. Per protocol, progression of study cancer was not a serious AE (SAE) unless related to study drug. MedDRA terms "Neoplasm progression", "Malignant neoplasm progression" & "Disease progression" unrelated to study drug are excluded as SAEs. Drug-related deaths are reported as "Malignant Neoplasm Progression".

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 20.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------------|
| Reporting group title | Active Comparator |
|-----------------------|-------------------|

Reporting group description:

Participants received methotrexate 40 mg/m² IV (may have been escalated to 60 mg/m² maximum dose) on Days 1, 8, and 15 of each 3-week cycle; or docetaxel 75 mg/m² IV on Day 1 of each 3-week cycle; or cetuximab 400 mg/m² IV loading dose on Day 1 and 250 mg/m² IV on Days 8 and 15 of Cycle 1, followed by cetuximab 250 mg/m² on Days 1, 8, and 15 of each subsequent 3-week cycle.

| | |
|-----------------------|---------------|
| Reporting group title | Pembrolizumab |
|-----------------------|---------------|

Reporting group description:

Participants received pembrolizumab 200 mg IV on Day 1 of each 3-week cycle.

| Serious adverse events | Active Comparator | Pembrolizumab | |
|---|-------------------|--------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 92 / 234 (39.32%) | 110 / 246 (44.72%) | |
| number of deaths (all causes) | 207 | 181 | |
| number of deaths resulting from adverse events | 2 | 4 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Astrocytoma, low grade | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colon cancer | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infected neoplasm | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 1 / 1 | 1 / 1 | |
| Paraneoplastic syndrome | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal cancer | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour haemorrhage | | | |
| subjects affected / exposed | 2 / 234 (0.85%) | 9 / 246 (3.66%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 10 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 2 | |
| Tumour pain | | | |
| subjects affected / exposed | 2 / 234 (0.85%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Angiodysplasia | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Deep vein thrombosis | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhage | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jugular vein thrombosis | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 4 / 234 (1.71%) | 5 / 246 (2.03%) | |
| occurrences causally related to treatment / all | 0 / 4 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 4 | 1 / 5 | |
| Euthanasia | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Face oedema | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ill-defined disorder | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (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 | 2 / 234 (0.85%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Performance status decreased | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 234 (1.28%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Asphyxia | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Aspiration | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 4 / 246 (1.63%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Eosinophilic pneumonia | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Laryngeal obstruction | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Laryngeal stenosis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung disorder | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pharyngeal fistula | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 3 / 234 (1.28%) | 6 / 246 (2.44%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 3 / 234 (1.28%) | 6 / 246 (2.44%) | |
| occurrences causally related to treatment / all | 0 / 3 | 4 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 2 / 234 (0.85%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Respiratory disorder | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Respiratory tract haemorrhage | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 1 / 246 (0.41%) | |
| 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 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 3 / 234 (1.28%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 5 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Platelet count decreased | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 2 / 234 (0.85%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Accidental overdose | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Alcohol poisoning | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Fall | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Postoperative fever | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Procedural hypotension | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal fracture | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stoma site haemorrhage | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stoma site ulcer | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tracheostomy malfunction | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pericardial effusion | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Guillain-Barre syndrome | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Somnolence | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal cord compression | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vocal cord paresis | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |

| | | | |
|---|-----------------|-----------------|--|
| Anaemia | | | |
| subjects affected / exposed | 2 / 234 (0.85%) | 5 / 246 (2.03%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anaemia of malignant disease | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 9 / 234 (3.85%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 8 / 9 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymph node haemorrhage | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 234 (0.85%) | 6 / 246 (2.44%) | |
| occurrences causally related to treatment / all | 2 / 2 | 5 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysphagia | | | |
| subjects affected / exposed | 3 / 234 (1.28%) | 4 / 246 (1.63%) | |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 2 / 234 (0.85%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal inflammation | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Incarcerated inguinal hernia | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestine perforation | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Malignant dysphagia | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mouth haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 3 / 234 (1.28%) | 3 / 246 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oral discharge | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumoperitoneum | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stomatitis | | | |
| subjects affected / exposed | 3 / 234 (1.28%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 3 / 3 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Autoimmune hepatitis | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cirrhosis alcoholic | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Acute febrile neutrophilic dermatosis | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fungating wound | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pruritus | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin ulcer | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stevens-Johnson syndrome | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Hypercalcaemia of malignancy | | | |
| subjects affected / exposed | 2 / 234 (0.85%) | 3 / 246 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Musculoskeletal and connective tissue disorders | | | |
| Kyphosis | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| 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 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Soft tissue haemorrhage | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Candida sepsis | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 3 / 246 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 2 / 234 (0.85%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colonic abscess | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Disseminated tuberculosis | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epiglottitis | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infected fistula | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (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 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infective exacerbation of chronic obstructive airways disease | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Klebsiella infection | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection bacterial | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infection | | | |
| subjects affected / exposed | 2 / 234 (0.85%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oral bacterial infection | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oral candidiasis | | | |
| subjects affected / exposed | 2 / 234 (0.85%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumocystis jirovecii pneumonia | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 16 / 234 (6.84%) | 20 / 246 (8.13%) | |
| occurrences causally related to treatment / all | 4 / 17 | 1 / 21 | |
| deaths causally related to treatment / all | 1 / 5 | 0 / 6 | |
| Pulmonary sepsis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 3 / 234 (1.28%) | 4 / 246 (1.63%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Stoma site infection | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 234 (0.85%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 234 (0.00%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound infection | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 4 / 246 (1.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 3 / 234 (1.28%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetes mellitus inadequate control | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 7 / 246 (2.85%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 3 / 246 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Active Comparator | Pembrolizumab | |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 210 / 234 (89.74%) | 212 / 246 (86.18%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour pain | | | |
| subjects affected / exposed | 7 / 234 (2.99%) | 13 / 246 (5.28%) | |
| occurrences (all) | 8 | 13 | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 12 / 234 (5.13%) | 12 / 246 (4.88%) | |
| occurrences (all) | 16 | 12 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 41 / 234 (17.52%) | 37 / 246 (15.04%) | |
| occurrences (all) | 52 | 47 | |
| Fatigue | | | |
| subjects affected / exposed | 63 / 234 (26.92%) | 48 / 246 (19.51%) | |
| occurrences (all) | 81 | 51 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 36 / 234 (15.38%) | 17 / 246 (6.91%) | |
| occurrences (all) | 51 | 21 | |
| Pyrexia | | | |
| subjects affected / exposed | 25 / 234 (10.68%) | 24 / 246 (9.76%) | |
| occurrences (all) | 35 | 38 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 36 / 234 (15.38%) | 42 / 246 (17.07%) | |
| occurrences (all) | 39 | 47 | |
| Dyspnoea | | | |
| subjects affected / exposed | 26 / 234 (11.11%) | 30 / 246 (12.20%) | |
| occurrences (all) | 31 | 32 | |
| Haemoptysis | | | |
| subjects affected / exposed | 6 / 234 (2.56%) | 13 / 246 (5.28%) | |
| occurrences (all) | 8 | 15 | |
| Productive cough | | | |

| | | | |
|--|----------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 5 / 234 (2.14%) 7 | 14 / 246 (5.69%) 14 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 6 / 234 (2.56%) | 13 / 246 (5.28%) | |
| occurrences (all) | 6 | 13 | |
| Insomnia | | | |
| subjects affected / exposed | 17 / 234 (7.26%) | 22 / 246 (8.94%) | |
| occurrences (all) | 17 | 22 | |
| Investigations | | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 13 / 234 (5.56%) | 10 / 246 (4.07%) | |
| occurrences (all) | 18 | 10 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 24 / 234 (10.26%) | 4 / 246 (1.63%) | |
| occurrences (all) | 29 | 11 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 13 / 234 (5.56%) | 7 / 246 (2.85%) | |
| occurrences (all) | 19 | 7 | |
| Weight decreased | | | |
| subjects affected / exposed | 26 / 234 (11.11%) | 21 / 246 (8.54%) | |
| occurrences (all) | 26 | 22 | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 12 / 234 (5.13%) | 2 / 246 (0.81%) | |
| occurrences (all) | 15 | 3 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 22 / 234 (9.40%) | 21 / 246 (8.54%) | |
| occurrences (all) | 24 | 25 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 51 / 234 (21.79%) | 62 / 246 (25.20%) | |
| occurrences (all) | 70 | 77 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |

| | | | |
|--|-------------------|-------------------|--|
| subjects affected / exposed | 12 / 234 (5.13%) | 9 / 246 (3.66%) | |
| occurrences (all) | 12 | 9 | |
| Constipation | | | |
| subjects affected / exposed | 37 / 234 (15.81%) | 43 / 246 (17.48%) | |
| occurrences (all) | 43 | 49 | |
| Diarrhoea | | | |
| subjects affected / exposed | 41 / 234 (17.52%) | 36 / 246 (14.63%) | |
| occurrences (all) | 50 | 54 | |
| Dry mouth | | | |
| subjects affected / exposed | 6 / 234 (2.56%) | 15 / 246 (6.10%) | |
| occurrences (all) | 6 | 15 | |
| Dysphagia | | | |
| subjects affected / exposed | 15 / 234 (6.41%) | 21 / 246 (8.54%) | |
| occurrences (all) | 16 | 23 | |
| Nausea | | | |
| subjects affected / exposed | 44 / 234 (18.80%) | 34 / 246 (13.82%) | |
| occurrences (all) | 52 | 43 | |
| Stomatitis | | | |
| subjects affected / exposed | 26 / 234 (11.11%) | 7 / 246 (2.85%) | |
| occurrences (all) | 34 | 9 | |
| Vomiting | | | |
| subjects affected / exposed | 23 / 234 (9.83%) | 23 / 246 (9.35%) | |
| occurrences (all) | 34 | 27 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 27 / 234 (11.54%) | 1 / 246 (0.41%) | |
| occurrences (all) | 27 | 1 | |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 18 / 234 (7.69%) | 0 / 246 (0.00%) | |
| occurrences (all) | 28 | 0 | |
| Dry skin | | | |
| subjects affected / exposed | 17 / 234 (7.26%) | 4 / 246 (1.63%) | |
| occurrences (all) | 19 | 4 | |
| Pruritus | | | |
| subjects affected / exposed | 17 / 234 (7.26%) | 18 / 246 (7.32%) | |
| occurrences (all) | 40 | 22 | |

| | | | |
|---|---|---|--|
| Rash subjects affected / exposed occurrences (all) | 38 / 234 (16.24%) 81 | 25 / 246 (10.16%) 32 | |
| Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all) | 9 / 234 (3.85%) 9 | 37 / 246 (15.04%) 40 | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Neck pain subjects affected / exposed occurrences (all) | 5 / 234 (2.14%) 6 8 / 234 (3.42%) 8 17 / 234 (7.26%) 17 | 19 / 246 (7.72%) 20 23 / 246 (9.35%) 24 19 / 246 (7.72%) 19 | |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hypercalcaemia subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all) Hypomagnesaemia subjects affected / exposed occurrences (all) Hyponatraemia subjects affected / exposed occurrences (all) Hypophosphataemia subjects affected / exposed occurrences (all) | 43 / 234 (18.38%) 48 13 / 234 (5.56%) 14 19 / 234 (8.12%) 21 20 / 234 (8.55%) 25 16 / 234 (6.84%) 17 12 / 234 (5.13%) 14 | 31 / 246 (12.60%) 37 14 / 246 (5.69%) 16 23 / 246 (9.35%) 27 10 / 246 (4.07%) 11 12 / 246 (4.88%) 14 15 / 246 (6.10%) 21 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 27 February 2015 | Amendment 01: Increased sample size from 466 to 600 participants, added hypotheses, and added statistical analyses for the PD-L1 Strong Positive (TPS >50% PD-L1) population; Inclusion/Exclusion criteria modifications were made to align with program standards. |
| 16 April 2016 | Amendment 10: Decreased the sample size from 600 to 466 subjects, downgraded OS in the PD-L1 positive subjects and PFS from primary hypotheses to key secondary hypotheses, replaced hypotheses on the PD-L1 population with hypotheses on the CPS ≥ 1 population, promoted ORR to the key secondary endpoints, updated language to include PD-L1 status masking, and included the role of unblended Sponsor personnel. |
| 02 November 2016 | Amendment 11: Updated, in the Statistical Analysis Plan, the alpha-spending language, power calculation, and timing of the final analysis to reflect the change to the number of death events at the final analysis. |
| 20 February 2018 | Amendment 12: Added text and updated Dose Modification Guidelines for Pembrolizumab and added text to enable survival follow-up activities throughout the study. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported