# Clinical trial results:
# A Randomized, Double-Blind, Phase 3 Study of Pemetrexed + Platinum Chemotherapy with or without Pembrolizumab (MK-3475) in TKI-resistant EGFR-mutated Tumors in Metastatic Non-squamous Non-small Cell Lung Cancer (NSCLC) Participants (KEYNOTE-789)

## Summary

| | |
|---|---|
| EudraCT number | 2017-004188-11 |
| Trial protocol | SE ES FR DE GB IT |
| Global end of trial date | 02 October 2023 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 10 October 2024 |
| First version publication date | 10 October 2024 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | 3475-789 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03515837 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

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

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 02 October 2023 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 17 January 2023 |
| Global end of trial reached? | Yes |
| Global end of trial date | 02 October 2023 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the efficacy and safety of pemetrexed plus platinum chemotherapy (carboplatin or cisplatin) with or without pembrolizumab (MK-3475; KEYTRUDA®) in the treatment of adults with the following types of tyrosine kinase inhibitor (TKI)-resistant, epidermal growth factor receptor (EGFR)-mutated, metastatic non-squamous non-small cell lung cancer (NSCLC) tumors: 1) TKI-failures (including osimertinib [TAGRISSO®] failure) with T790M-negative mutation tumors, 2) T790M-positive mutation tumors with prior exposure to osimertinib, and 3) first-line osimertinib failure regardless of T790M mutation status.

The primary study hypotheses are that the combination of pembrolizumab plus chemotherapy has superior efficacy compared to saline placebo plus chemotherapy in terms of Progression-free Survival (PFS) and Overall Survival (OS).

Upon study completion, participants are discontinued and may be enrolled in a pembrolizumab extension study, if available.

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 | 29 June 2018 |
| 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: 14 |
| Country: Number of subjects enrolled | Brazil: 9 |
| Country: Number of subjects enrolled | Canada: 20 |
| Country: Number of subjects enrolled | China: 112 |
| Country: Number of subjects enrolled | France: 16 |
| Country: Number of subjects enrolled | Germany: 7 |
| Country: Number of subjects enrolled | Hong Kong: 13 |
| Country: Number of subjects enrolled | Israel: 17 |
| Country: Number of subjects enrolled | Italy: 28 |
| Country: Number of subjects enrolled | Japan: 79 |
| Country: Number of subjects enrolled | Korea, Republic of: 52 |

| | |
|---|---|
| Country: Number of subjects enrolled | Mexico: 23 |
| Country: Number of subjects enrolled | Spain: 28 |
| Country: Number of subjects enrolled | Sweden: 11 |
| Country: Number of subjects enrolled | Taiwan: 44 |
| Country: Number of subjects enrolled | United Kingdom: 10 |
| Country: Number of subjects enrolled | United States: 9 |
| Worldwide total number of subjects | 492 |
| EEA total number of subjects | 90 |

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) | 272 |
| From 65 to 84 years | 218 |
| 85 years and over | 2 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Of 855 participants screened, 492 randomized; of these, 491 received treatment.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Pembro + Pemetrexed + Chemo |

Arm description:

Participants received pembrolizumab (pembro) 200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles PLUS pemetrexed 500 mg/m^2 via IV infusion Q3W with no restrictions on the number of cycles PLUS platinum chemotherapy (chemo) (either carboplatin Area Under the Curve [AUC] 5 via IV infusion Q3W for 4 cycles [Cycles 1-4] or cisplatin 75 mg/m^2 via IV infusion Q3W for 4 cycles [Cycles 1-4]).

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Pemetrexed |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

500 mg/m^2 via IV infusion Q3W with no restrictions on the number of cycles

| | |
|---|---|
| Investigational medicinal product name | Cisplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

75 mg/m^2 via IV infusion Q3W for 4 cycles (Cycles 1-4).

| | |
|---|---|
| Investigational medicinal product name | Carboplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Area Under the Curve (AUC) 5 via IV infusion Q3W for 4 cycles (Cycles 1-4)

| | |
|---|---|
| Investigational medicinal product name | Pembrolizumab |
| Investigational medicinal product code | |
| Other name | MK-3475,<br>SCH-900475,<br>KEYTRUDA® |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles

| **Arm title** | Placebo + Pemetrexed + Chemo |
|---|---|

Arm description:

Participants received normal saline solution via IV infusion on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles PLUS pemetrexed 500 mg/m^2 via IV infusion Q3W with no restrictions on the number of cycles PLUS platinum chemotherapy (chemo)(either carboplatin AUC 5 via IV infusion Q3W for 4 cycles [Cycles 1-4] or cisplatin 75 mg/m^2 via IV infusion Q3W for 4 cycles [Cycles 1-4]). Eligible participants who had BICR-verified progressive disease were eligible to switch over to pembrolizumab monotherapy 200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles.

| Arm type | Placebo |
|---|---|
| Investigational medicinal product name | Saline placebo to pembrolizumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Saline placebo administered via IV infusion on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles

| Investigational medicinal product name | Pemetrexed |
|---|---|
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

500 mg/m^2 via IV infusion Q3W with no restrictions on the number of cycles

| Investigational medicinal product name | Pembrolizumab |
|---|---|
| Investigational medicinal product code | |
| Other name | MK-3475,<br>SCH-900475,<br>KEYTRUDA® |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

After meeting protocol requirements for ending placebo treatment, pembrolizumab could have been administered 200 mg via IV infusion Q3W for up to 35 cycles

| Investigational medicinal product name | Cisplatin |
|---|---|
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

75 mg/m^2 via IV infusion Q3W for 4 cycles (Cycles 1-4).

| Investigational medicinal product name | Carboplatin |
|---|---|
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Area Under the Curve (AUC) 5 via IV infusion Q3W for 4 cycles (Cycles 1-4)

| **Number of subjects in period 1** | Pembro + Pemetrexed + Chemo | Placebo + Pemetrexed + Chemo |
|---|---|---|
| Started | 245 | 247 |
| Treated | 245 | 246 |
| Switched over to Pembro monotherapy | 0 | 50 |
| Completed | 0 | 0 |
| Not completed | 245 | 247 |
| Adverse event, serious fatal | 219 | 227 |
| Consent withdrawn by subject | - | 4 |
| Participation Was Terminated By Sponsor | 26 | 15 |
| Lost to follow-up | - | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Pembro + Pemetrexed + Chemo |
| Reporting group description: | |
| Participants received pembrolizumab (pembro) 200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles PLUS pemetrexed 500 mg/m^2 via IV infusion Q3W with no restrictions on the number of cycles PLUS platinum chemotherapy (chemo) (either carboplatin Area Under the Curve [AUC] 5 via IV infusion Q3W for 4 cycles [Cycles 1-4] or cisplatin 75 mg/m^2 via IV infusion Q3W for 4 cycles [Cycles 1-4]). | |
| Reporting group title | Placebo + Pemetrexed + Chemo |
| Reporting group description: | |
| Participants received normal saline solution via IV infusion on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles PLUS pemetrexed 500 mg/m^2 via IV infusion Q3W with no restrictions on the number of cycles PLUS platinum chemotherapy (chemo)(either carboplatin AUC 5 via IV infusion Q3W for 4 cycles [Cycles 1-4] or cisplatin 75 mg/m^2 via IV infusion Q3W for 4 cycles [Cycles 1-4]). Eligible participants who had BICR-verified progressive disease were eligible to switch over to pembrolizumab monotherapy 200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles. | |

| **Reporting group values** | Pembro + Pemetrexed + Chemo | Placebo + Pemetrexed + Chemo | Total |
|---|---|---|---|
| Number of subjects | 245 | 247 | 492 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 146 | 126 | 272 |
| From 65-84 years | 97 | 121 | 218 |
| 85 years and over | 2 | 0 | 2 |
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | 61.7 | 63.1 | |
| standard deviation | ± 10.9 | ± 10.0 | - |
| Sex: Female, Male<br>Units: Participants | | | |
| Female | 152 | 151 | 303 |
| Male | 93 | 96 | 189 |
| Race (NIH/OMB)<br>Units: Subjects | | | |
| American Indian or Alaska Native | 3 | 3 | 6 |
| Asian | 165 | 163 | 328 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 2 | 5 | 7 |
| White | 67 | 72 | 139 |
| More than one race | 1 | 0 | 1 |

| | | | |
|---|---|---|---|
| Unknown or Not Reported | 7 | 4 | 11 |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 16 | 19 | 35 |
| Not Hispanic or Latino | 222 | 221 | 443 |
| Unknown or Not Reported | 7 | 7 | 14 |
| Previous use of Tyrosine Kinase Inhibitor (TKI) Treatment History with Osimertinib | | | |
| Participants were stratified using previous treatment history with TKI osimertinib: osimertinib or no osimertinib. | | | |
| Units: Subjects | | | |
| Treated with TKI except for Osimertinib | 128 | 126 | 254 |
| Treated with first line Osimertinib | 28 | 33 | 61 |
| Treated with second line Osimertinib | 88 | 88 | 176 |
| Other | 1 | 0 | 1 |
| Geographic Region: East Asia | | | |
| Participants were stratified by geographic area of the enrolling site: East Asia versus Non-East Asia | | | |
| Units: Subjects | | | |
| East Asia | 150 | 150 | 300 |
| Non-East Asia | 95 | 97 | 192 |
| Geographic Region: US | | | |
| Participants were stratified by geographic area of the enrolling site: United States versus Non-United States | | | |
| Units: Subjects | | | |
| US | 3 | 6 | 9 |
| Non-EU | 242 | 241 | 483 |
| Geographic Region: EU | | | |
| Participants were stratified by geographic area of the enrolling site: European Union versus Non-European Union | | | |
| Units: Subjects | | | |
| EU | 53 | 47 | 100 |
| Non-EU | 192 | 200 | 392 |
| Programmed Death Ligand 1 (PD-L1) Status | | | |
| Participants were assessed for their PD-L1 tumor expression level by immunohistochemistry assay using tumor tissue from a newly obtained biopsy. PD-L1 status is determined by tumor proportion score (TPS). 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 ≥ 50% | 52 | 51 | 103 |
| TPS <50% | 181 | 185 | 366 |
| Not evaluable | 12 | 11 | 23 |
| Programmed Death Ligand 1 Status | | | |
| Participants were assessed for their PD-L1 tumor expression level by immunohistochemistry assay using tumor tissue from a newly obtained biopsy. PD-L1 status is determined by tumor proportion score (TPS). 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 ≥ 50% | 52 | 51 | 103 |
| TPS ≥1% AND ≤49% | 54 | 72 | 126 |
| TPS <1% | 127 | 113 | 240 |
| Not evaluable | 12 | 11 | 23 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Pembro + Pemetrexed + Chemo |

Reporting group description:

Participants received pembrolizumab (pembro) 200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles PLUS pemetrexed 500 mg/m^2 via IV infusion Q3W with no restrictions on the number of cycles PLUS platinum chemotherapy (chemo) (either carboplatin Area Under the Curve [AUC] 5 via IV infusion Q3W for 4 cycles [Cycles 1-4] or cisplatin 75 mg/m^2 via IV infusion Q3W for 4 cycles [Cycles 1-4]).

| | |
|---|---|
| Reporting group title | Placebo + Pemetrexed + Chemo |

Reporting group description:

Participants received normal saline solution via IV infusion on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles PLUS pemetrexed 500 mg/m^2 via IV infusion Q3W with no restrictions on the number of cycles PLUS platinum chemotherapy (chemo)(either carboplatin AUC 5 via IV infusion Q3W for 4 cycles [Cycles 1-4] or cisplatin 75 mg/m^2 via IV infusion Q3W for 4 cycles [Cycles 1-4]). Eligible participants who had BICR-verified progressive disease were eligible to switch over to pembrolizumab monotherapy 200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles.

### Primary: Progression-free Survival (PFS) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

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

End point description:

PFS is defined as the time from randomization to the first documented progressive disease (PD) or death due to any cause, whichever occurs first. PFS was assessed by blinded independent central review (BICR) using RECIST 1.1. Per RECIST 1.1, PD is 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 demonstrate an absolute increase of at least 5 mm. Note: The appearance of one or more new lesions is also considered PD. The PFS presented was analyzed using the product-limit (Kaplan-Meier) method for censored data. The analysis population included all randomized participants who received at least 1 dose of study intervention.

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

End point timeframe:

Up to ~40 months

| End point values | Pembro + Pemetrexed + Chemo | Placebo + Pemetrexed + Chemo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 245 | 247 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 5.6 (5.5 to 5.8) | 5.5 (5.4 to 5.6) | | |

### Statistical analyses

| | |
|---|---|
| **Statistical analysis title** | Hazard Ratio (HR) |

Statistical analysis description:

Hazard ratio with "Pembro + Pemetrexed + Chemo" as numerator and "Placebo + Pemetrexed +

Chemo" as denominator. Hazard ratio based on Cox regression model with Efron’s method of tie handling with treatment as a covariate stratified by PD-L1 expression; treatment history; geographic region of the enrolling site.

| | |
|---|---|
| Comparison groups | Pembro + Pemetrexed + Chemo v Placebo + Pemetrexed + Chemo |
| Number of subjects included in analysis | 492 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0122 [1] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.65 |
| upper limit | 0.97 |

Notes:

[1] - One-sided p-value based on log-rank test stratified by PD-L1 expression; treatment history; geographic region of the enrolling site.

## Primary: Overall Survival (OS)

| | |
|---|---|
| End point title | Overall Survival (OS) |

End point description:

OS is 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 presented was analyzed using the product-limit (Kaplan-Meier) method for censored data. The analysis population included all randomized participants who received at least 1 dose of study intervention.

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

End point timeframe:

Up to ~51 months

| **End point values** | Pembro + Pemetrexed + Chemo | Placebo + Pemetrexed + Chemo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 245 | 247 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 15.9 (13.7 to 18.8) | 14.7 (12.7 to 17.1) | | |

## Statistical analyses

| **Statistical analysis title** | Hazard Ratio (HR) |
|---|---|

Statistical analysis description:

Hazard ratio with "Pembro + Pemetrexed + Chemo" as numerator and "Placebo + Pemetrexed + Chemo" as denominator. Hazard ratio based on Cox regression model with Efron’s method of tie handling with treatment as a covariate stratified by PD-L1 expression; treatment history; geographic region of the enrolling site.

| | |
|---|---|
| Comparison groups | Pembro + Pemetrexed + Chemo v Placebo + Pemetrexed + |

| | Chemo |
|---|---|
| Number of subjects included in analysis | 492 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0362 [2] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.84 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.69 |
| upper limit | 1.02 |

Notes:

[2] - One-sided p-value based on log-rank test stratified by PD-L1 expression; treatment history; geographic region of the enrolling site.

## Secondary: Objective Response Rate (ORR) Per RECIST 1.1

| End point title | Objective Response Rate (ORR) Per RECIST 1.1 |
|---|---|

End point description:

ORR was assessed by BICR using RECIST 1.1. ORR is defined as the percentage of participants in the analysis population who experience 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, taking as reference the baseline sum diameters) per RECIST 1.1. The ORR for participants is presented. The analysis population included all randomized participants who received at least 1 dose of study intervention.

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

End point timeframe:

Up to ~51 months

| **End point values** | Pembro + Pemetrexed + Chemo | Placebo + Pemetrexed + Chemo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 245 | 247 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 29.0 (23.4 to 35.1) | 27.1 (21.7 to 33.1) | | |

## Statistical analyses

| **Statistical analysis title** | Mean Difference (Final Values) |
|---|---|

Statistical analysis description:

Mean difference in final values: "Pembro + Pemetrexed + Chemo" minus "Placebo + Pemetrexed + Chemo". Based on Miettinen & Nurminen method stratified by PD-L1 expression; treatment history; geographic region of the enrolling site.

| Comparison groups | Pembro + Pemetrexed + Chemo v Placebo + Pemetrexed + Chemo |
|---|---|

| | |
|---|---|
| Number of subjects included in analysis | 492 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6 |
| upper limit | 9.9 |

## Secondary: Duration of Response (DOR) Per RECIST 1.1

| | |
|---|---|
| End point title | Duration of Response (DOR) Per RECIST 1.1 |

End point description:

DOR was assessed by BICR using RECIST 1.1. For participants who experience a response of CR or PR, DOR is defined as the time from the earliest date of qualifying response until earliest date of PD or death from any cause, whichever comes first. The DOR presented was analyzed using the product-limit (Kaplan-Meier) method for censored data. The analysis population included all randomized participants who received at least 1 dose of study intervention.

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

End point timeframe:

Up to ~51 months

| **End point values** | Pembro + Pemetrexed + Chemo | Placebo + Pemetrexed + Chemo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 245 | 246 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 6.3 (5.9 to 8.3) | 5.6 (4.4 to 6.3) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) Global Health Status (Item 29) and Quality of Life (Item 30) Combined Score

| | |
|---|---|
| End point title | Change from Baseline in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) Global Health Status (Item 29) and Quality of Life (Item 30) Combined Score |

End point description:

The EORTC QLQ-C30 is a questionnaire to assess the overall quality of life of cancer patients. Participant responses to the questions regarding Global Health Status (GHS; "How would you rate your overall health during the past week?") and Quality of Life (QoL; "How would you rate your overall quality of life during the past week?") are each scored on a 7-point scale (1=Very poor to 7=Excellent). The two raw scores were averaged into a combined score, then normalized using linear transformation so each

participant's score ranged from 0 to 100 (0=Worst overall health/quality of life and 100=Best overall health/quality of life). The change from baseline in GHS (EORTC QLQ-C30 Item 29) and QoL (EORTC QLQ-C30 Item 30) combined score is presented. The analysis population included all randomized participants who had at least 1 patient reported outcome (PRO) assessment available and had received at least 1 dose of study intervention.

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

End point timeframe:

Baseline and Week 18

| **End point values** | Pembro + Pemetrexed + Chemo | Placebo + Pemetrexed + Chemo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 241 | 243 | | |
| Units: Score on a Scale | | | | |
| least squares mean (confidence interval 95%) | -0.46 (-3.17 to 2.25) | -2.05 (-4.74 to 0.64) | | |

**Statistical analyses**

| **Statistical analysis title** | Difference in Least Squares (LS) Means |
|---|---|

Statistical analysis description:

Difference in LS Means: "Pembro + Pemetrexed + Chemo" minus "Placebo + Pemetrexed + Chemo". Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by time interaction, stratification factors PD-L1 expression, treatment history, and geographic region of the enrolling site as covariates.

| Comparison groups | Pembro + Pemetrexed + Chemo v Placebo + Pemetrexed + Chemo |
|---|---|
| Number of subjects included in analysis | 484 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Difference in LS Means |
| Point estimate | 1.59 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.93 |
| upper limit | 5.1 |

**Secondary: Time to True Deterioration (TTD) in the EORTC Questionnaire Composite Endpoint of Cough, Chest Pain or Dyspnea**

| End point title | Time to True Deterioration (TTD) in the EORTC Questionnaire Composite Endpoint of Cough, Chest Pain or Dyspnea |
|---|---|

End point description:

TTD is the time from baseline to first onset of 10 points or more deterioration from baseline with confirmation by the subsequent visit of 10 points or more deterioration from baseline in the composite endpoint of cough [EORTC QLQ-Lung Cancer Module 13 (LC13) Item 1; How much did you cough?], chest pain [EORTC QLQ-LC13 Item 10; Have you had pain in your chest?], or dyspnea [EORTC QLQ-C30 Item 8; Were you short of breath?]. Individual responses are given on a 4-point scale (1=Not at all;

4=Very much), with a lower score indicating a better outcome. TTD was analyzed using the product-limit (Kaplan-Meier) method for censored data. The time to true deterioration in the composite endpoint of cough, chest pain or dyspnea is presented. The analysis population included all randomized participants who had at least 1 patient reported outcome (PRO) assessment available and had received at least 1 dose of study intervention. 9999 = Median and/or upper range time to deterioration were not reached.

| End point type | Secondary |
|---|---|
| End point timeframe: | |
| Baseline and up to ~51 months | |

| **End point values** | Pembro + Pemetrexed + Chemo | Placebo + Pemetrexed + Chemo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 237 | 236 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 9999 (10.05 to 9999) | 17.97 (6.67 to 9999) | | |

## Statistical analyses

| **Statistical analysis title** | Hazard Ratio (HR) |
|---|---|

Statistical analysis description:

Hazard ratio with "Pembro + Pemetrexed + Chemo" as numerator and "Placebo + Pemetrexed + Chemo" as denominator. Hazard ratio based on Cox regression model with Efron’s method of tie handling with treatment as a covariate stratified by PD-L1 expression; treatment history; geographic region of the enrolling site.

| Comparison groups | Pembro + Pemetrexed + Chemo v Placebo + Pemetrexed + Chemo |
|---|---|
| Number of subjects included in analysis | 473 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.93 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.68 |
| upper limit | 1.27 |

## Secondary: Percentage of participants who experienced an adverse event (AE)

| End point title | Percentage of participants who experienced an adverse event (AE) |
|---|---|

End point description:

An AE is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the study treatment, whether or not considered related to the use of study treatment. The percentage of participants who experienced an AE is presented. The analysis population included all randomized participants who received at least 1 dose of study intervention.

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

End point timeframe:

Up to ~44 months

| End point values | Pembro + Pemetrexed + Chemo | Placebo + Pemetrexed + Chemo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 245 | 246 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 97.6 | 98.0 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants who Discontinued Study Treatment Due to AEs

| End point title | Percentage of Participants who Discontinued Study Treatment Due to AEs |
|---|---|

End point description:

An AE is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the study treatment, whether or not considered related to the use of study treatment. The percentage of participants who discontinued study treatment due to an adverse event is presented. The analysis population included all randomized participants who received at least 1 dose of study intervention.

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

End point timeframe:

Up to ~41 months

| End point values | Pembro + Pemetrexed + Chemo | Placebo + Pemetrexed + Chemo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 245 | 246 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 19.2 | 17.1 | | |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to ~59 months

Adverse event reporting additional description:

AEs include all participants who received ≥1 dose of study drug. Deaths include all randomized participants. Per protocol, progression of cancer under study was not an AE unless related to study treatment. Thus, MedDRA terms "Neoplasm progression", "Malignant neoplasm progression" & "Disease progression" not related to treatment are excluded as AEs

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 26.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Pembro + Pemetrexed + Chemo |

Reporting group description:

Participants received pembrolizumab (pembro) 200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles PLUS pemetrexed 500 mg/m^2 via IV infusion Q3W with no restrictions on the number of cycles PLUS platinum chemotherapy (chemo) (either carboplatin Area Under the Curve [AUC] 5 via IV infusion Q3W for 4 cycles [Cycles 1-4] or cisplatin 75 mg/m^2 via IV infusion Q3W for 4 cycles [Cycles 1-4]).

| | |
|---|---|
| Reporting group title | Placebo +Pemetrexed +Chemo Switched Over to Pembro monotherapy |

Reporting group description:

Participants who received placebo + pemetrexed + chemo per their randomized treatment assignment and had BICR-verified progressive disease were eligible to receive pembrolizumab monotherapy 200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles.

| | |
|---|---|
| Reporting group title | Placebo + Pemetrexed + Chemo |

Reporting group description:

Participants received normal saline solution via IV infusion on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles PLUS pemetrexed 500 mg/m^2 via IV infusion Q3W with no restrictions on the number of cycles PLUS platinum chemotherapy (chemo)(either carboplatin AUC 5 via IV infusion Q3W for 4 cycles [Cycles 1-4] or cisplatin 75 mg/m^2 via IV infusion Q3W for 4 cycles [Cycles 1-4]). Eligible participants who had BICR-verified progressive disease were eligible to switch over to pembrolizumab monotherapy 200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles.

| **Serious adverse events** | Pembro + Pemetrexed + Chemo | Placebo +Pemetrexed +Chemo Switched Over to Pembro monotherapy | Placebo + Pemetrexed + Chemo |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 86 / 245 (35.10%) | 8 / 50 (16.00%) | 70 / 246 (28.46%) |
| number of deaths (all causes) | 219 | 44 | 186 |
| number of deaths resulting from adverse events | 5 | 0 | 12 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Small cell lung cancer | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Breast cancer | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute myeloid leukaemia | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 1 / 50 (2.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Death | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |

| | | | |
|---|---|---|---|
| Sudden death | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Pyrexia | | | |
| subjects affected / exposed | 5 / 245 (2.04%) | 1 / 50 (2.00%) | 4 / 246 (1.63%) |
| occurrences causally related to treatment / all | 2 / 5 | 0 / 1 | 2 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malaise | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 3 / 246 (1.22%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Fatigue | | | |
| subjects affected / exposed | 2 / 245 (0.82%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Prostatomegaly | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemothorax | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 7 / 245 (2.86%) | 0 / 50 (0.00%) | 4 / 246 (1.63%) |
| occurrences causally related to treatment / all | 1 / 7 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune-mediated lung disease | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 1 / 50 (2.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 2 / 246 (0.81%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 2 / 246 (0.81%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Pneumothorax | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 2 / 245 (0.82%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleuritic pain | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hallucination | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 4 / 245 (1.63%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 4 / 245 (1.63%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 5 / 245 (2.04%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 5 / 5 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Platelet count decreased | | | |
| subjects affected / exposed | 8 / 245 (3.27%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 9 / 9 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 5 / 245 (2.04%) | 0 / 50 (0.00%) | 2 / 246 (0.81%) |
| occurrences causally related to treatment / all | 5 / 5 | 0 / 0 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| White blood cell count increased | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 1 / 50 (2.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Cervical vertebral fracture | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Craniocerebral injury | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femoral neck fracture | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fracture | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Hip fracture | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple fractures | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Road traffic accident | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Spinal fracture | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subdural haematoma | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular access complication | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Atrial flutter | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac arrest | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Cardiac tamponade | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericardial effusion | | | |
| subjects affected / exposed | 2 / 245 (0.82%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocarditis | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 5 / 245 (2.04%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 2 / 5 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral infarction | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 3 / 246 (1.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral haematoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cognitive disorder | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorder | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Generalised tonic-clonic seizure | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal cord compression | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 2 / 246 (0.81%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stroke in evolution | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Status epilepticus | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vocal cord paresis | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Blood and lymphatic system disorders** | | | |
| Anaemia | | | |
| subjects affected / exposed | 6 / 245 (2.45%) | 0 / 50 (0.00%) | 8 / 246 (3.25%) |
| occurrences causally related to treatment / all | 6 / 6 | 0 / 0 | 5 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bone marrow failure | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 4 / 245 (1.63%) | 0 / 50 (0.00%) | 2 / 246 (0.81%) |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Ear and labyrinth disorders** | | | |

| | | | |
|---|---|---|---|
| Vertigo | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meniere's disease | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Retinal detachment | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Macular hole | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cataract | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ascites | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Constipation | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 2 / 245 (0.82%) | 0 / 50 (0.00%) | 3 / 246 (1.22%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 4 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mesenteric artery thrombosis | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhoids | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematemesis | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulum intestinal | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 245 (0.82%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal ulcer haemorrhage | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 2 / 245 (0.82%) | 0 / 50 (0.00%) | 5 / 246 (2.03%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 5 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Hepatitis acute | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Autoimmune hepatitis | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|---|---|---|
| Lichenoid keratosis | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Drug eruption | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 1 / 50 (2.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Tubulointerstitial nephritis | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune-mediated nephritis | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematuria | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 1 / 50 (2.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myositis | | | |
| subjects affected / exposed | 2 / 245 (0.82%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Flank pain | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bone pain | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Bacteraemia | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pseudomembranous colitis | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection | | | |
| subjects affected / exposed | 2 / 245 (0.82%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia bacteraemia | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erysipelas | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 4 / 246 (1.63%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 2 / 246 (0.81%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device related infection | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 50 (0.00%) | 2 / 246 (0.81%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 8 / 245 (3.27%) | 1 / 50 (2.00%) | 5 / 246 (2.03%) |
| occurrences causally related to treatment / all | 1 / 8 | 0 / 1 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| Endocarditis | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin infection | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Systemic infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 245 (0.82%) | 0 / 50 (0.00%) | 2 / 246 (0.81%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 1 / 50 (2.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fulminant type 1 diabetes mellitus | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 50 (0.00%) | 0 / 246 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Decreased appetite | | | |
| subjects affected / exposed | 4 / 245 (1.63%) | 0 / 50 (0.00%) | 1 / 246 (0.41%) |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| **Non-serious adverse events** | Pembro + Pemetrexed + Chemo | Placebo +Pemetrexed +Chemo Switched Over to Pembro monotherapy | Placebo + Pemetrexed + Chemo |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 233 / 245 (95.10%) | 31 / 50 (62.00%) | 225 / 246 (91.46%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 11 / 245 (4.49%) | 0 / 50 (0.00%) | 14 / 246 (5.69%) |
| occurrences (all) | 16 | 0 | 15 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 29 / 245 (11.84%) | 0 / 50 (0.00%) | 28 / 246 (11.38%) |
| occurrences (all) | 41 | 0 | 31 |
| Chest pain | | | |
| subjects affected / exposed | 17 / 245 (6.94%) | 3 / 50 (6.00%) | 9 / 246 (3.66%) |
| occurrences (all) | 17 | 3 | 10 |
| Fatigue | | | |
| subjects affected / exposed | 60 / 245 (24.49%) | 1 / 50 (2.00%) | 49 / 246 (19.92%) |
| occurrences (all) | 81 | 1 | 81 |
| Malaise | | | |
| subjects affected / exposed | 18 / 245 (7.35%) | 1 / 50 (2.00%) | 23 / 246 (9.35%) |
| occurrences (all) | 31 | 1 | 30 |
| Oedema peripheral | | | |
| subjects affected / exposed | 28 / 245 (11.43%) | 1 / 50 (2.00%) | 24 / 246 (9.76%) |
| occurrences (all) | 42 | 2 | 28 |
| Pyrexia | | | |
| subjects affected / exposed | 33 / 245 (13.47%) | 3 / 50 (6.00%) | 21 / 246 (8.54%) |
| occurrences (all) | 54 | 3 | 29 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 21 / 245 (8.57%) | 2 / 50 (4.00%) | 21 / 246 (8.54%) |
| occurrences (all) | 22 | 2 | 24 |
| Cough | | | |
| subjects affected / exposed | 41 / 245 (16.73%) | 5 / 50 (10.00%) | 32 / 246 (13.01%) |
| occurrences (all) | 54 | 5 | 36 |
| Psychiatric disorders | | | |

| | | | |
|---|---|---|---|
| Insomnia | | | |
| subjects affected / exposed | 23 / 245 (9.39%) | 1 / 50 (2.00%) | 17 / 246 (6.91%) |
| occurrences (all) | 24 | 1 | 17 |
| Investigations | | | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 19 / 245 (7.76%) | 4 / 50 (8.00%) | 13 / 246 (5.28%) |
| occurrences (all) | 26 | 5 | 14 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 24 / 245 (9.80%) | 3 / 50 (6.00%) | 20 / 246 (8.13%) |
| occurrences (all) | 32 | 3 | 23 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 55 / 245 (22.45%) | 3 / 50 (6.00%) | 55 / 246 (22.36%) |
| occurrences (all) | 98 | 3 | 83 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 60 / 245 (24.49%) | 3 / 50 (6.00%) | 58 / 246 (23.58%) |
| occurrences (all) | 96 | 5 | 82 |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 16 / 245 (6.53%) | 0 / 50 (0.00%) | 11 / 246 (4.47%) |
| occurrences (all) | 20 | 0 | 12 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 90 / 245 (36.73%) | 2 / 50 (4.00%) | 113 / 246 (45.93%) |
| occurrences (all) | 236 | 2 | 282 |
| Platelet count decreased | | | |
| subjects affected / exposed | 49 / 245 (20.00%) | 0 / 50 (0.00%) | 52 / 246 (21.14%) |
| occurrences (all) | 81 | 0 | 94 |
| Weight decreased | | | |
| subjects affected / exposed | 24 / 245 (9.80%) | 3 / 50 (6.00%) | 16 / 246 (6.50%) |
| occurrences (all) | 29 | 3 | 18 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 71 / 245 (28.98%) | 2 / 50 (4.00%) | 87 / 246 (35.37%) |
| occurrences (all) | 211 | 2 | 259 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 29 / 245 (11.84%) | 0 / 50 (0.00%) | 31 / 246 (12.60%) |
| occurrences (all) | 32 | 0 | 33 |
| Dysgeusia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 16 / 245 (6.53%) | 0 / 50 (0.00%) | 6 / 246 (2.44%) |
| occurrences (all) | 35 | 0 | 7 |
| Dizziness | | | |
| subjects affected / exposed | 22 / 245 (8.98%) | 1 / 50 (2.00%) | 23 / 246 (9.35%) |
| occurrences (all) | 42 | 1 | 38 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 99 / 245 (40.41%) | 4 / 50 (8.00%) | 110 / 246 (44.72%) |
| occurrences (all) | 161 | 4 | 177 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 9 / 245 (3.67%) | 2 / 50 (4.00%) | 15 / 246 (6.10%) |
| occurrences (all) | 9 | 2 | 15 |
| Nausea | | | |
| subjects affected / exposed | 96 / 245 (39.18%) | 4 / 50 (8.00%) | 107 / 246 (43.50%) |
| occurrences (all) | 242 | 4 | 237 |
| Diarrhoea | | | |
| subjects affected / exposed | 24 / 245 (9.80%) | 0 / 50 (0.00%) | 18 / 246 (7.32%) |
| occurrences (all) | 27 | 0 | 23 |
| Constipation | | | |
| subjects affected / exposed | 81 / 245 (33.06%) | 1 / 50 (2.00%) | 76 / 246 (30.89%) |
| occurrences (all) | 124 | 1 | 103 |
| Vomiting | | | |
| subjects affected / exposed | 48 / 245 (19.59%) | 5 / 50 (10.00%) | 44 / 246 (17.89%) |
| occurrences (all) | 61 | 5 | 55 |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 12 / 245 (4.90%) | 3 / 50 (6.00%) | 14 / 246 (5.69%) |
| occurrences (all) | 17 | 3 | 16 |
| Pruritus | | | |
| subjects affected / exposed | 17 / 245 (6.94%) | 3 / 50 (6.00%) | 13 / 246 (5.28%) |
| occurrences (all) | 18 | 3 | 15 |
| Endocrine disorders | | | |
| Hyperthyroidism | | | |
| subjects affected / exposed | 13 / 245 (5.31%) | 0 / 50 (0.00%) | 3 / 246 (1.22%) |
| occurrences (all) | 25 | 0 | 4 |
| Hypothyroidism | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 14 / 245 (5.71%) | 3 / 50 (6.00%) | 6 / 246 (2.44%) |
| occurrences (all) | 18 | 3 | 9 |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity | | | |
| subjects affected / exposed | 10 / 245 (4.08%) | 0 / 50 (0.00%) | 17 / 246 (6.91%) |
| occurrences (all) | 10 | 0 | 19 |
| Back pain | | | |
| subjects affected / exposed | 25 / 245 (10.20%) | 3 / 50 (6.00%) | 25 / 246 (10.16%) |
| occurrences (all) | 36 | 3 | 29 |
| Arthralgia | | | |
| subjects affected / exposed | 19 / 245 (7.76%) | 4 / 50 (8.00%) | 21 / 246 (8.54%) |
| occurrences (all) | 20 | 4 | 22 |
| Infections and infestations | | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 11 / 245 (4.49%) | 2 / 50 (4.00%) | 18 / 246 (7.32%) |
| occurrences (all) | 12 | 2 | 21 |
| Urinary tract infection | | | |
| subjects affected / exposed | 18 / 245 (7.35%) | 0 / 50 (0.00%) | 13 / 246 (5.28%) |
| occurrences (all) | 19 | 0 | 13 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 64 / 245 (26.12%) | 4 / 50 (8.00%) | 61 / 246 (24.80%) |
| occurrences (all) | 81 | 4 | 79 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 14 / 245 (5.71%) | 2 / 50 (4.00%) | 18 / 246 (7.32%) |
| occurrences (all) | 16 | 2 | 32 |
| Hypokalaemia | | | |
| subjects affected / exposed | 16 / 245 (6.53%) | 3 / 50 (6.00%) | 13 / 246 (5.28%) |
| occurrences (all) | 25 | 3 | 19 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 11 / 245 (4.49%) | 3 / 50 (6.00%) | 12 / 246 (4.88%) |
| occurrences (all) | 13 | 3 | 14 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 26 September 2018 | Amendment 3: Updated the Inclusion Criteria regarding creatinine clearance in order to align with regulatory safety labeling for pemetrexed. |
| 24 March 2020 | Amendment 4: Based on better understanding of survival outcomes for this population, planned statistical analyses were modified to relax superiority statistics without the need to alter population size. Part of the changes included removal of the Objective Response Rate-only interim analysis. |
| 23 February 2021 | Amendment 5: The control assumption for the planned Overall Survival analysis was updated to better reflect the characteristics of the population that was actually enrolled. The number and timing of analyses has also been updated based on actual enrollment timing. |
| 19 July 2021 | Amendment 6: The dose modification and toxicity management guidelines for immune-related adverse events (irAEs) were updated. |
| 11 October 2022 | Amendment 7: Text was added to specify that interim analysis 3 would become the final analysis if the observed number of events was too close to the target number of events for final analysis. |
| 23 August 2023 | Amendment 8: Text was added to allow participants to rollover to the extension study (MK-3475-587). |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported