



Clinical trial results:

A Phase II Trial to Investigate Genetic Markers of Response to Pembrolizumab (MK-3475, SCH 900475) Combined with Chemotherapy as a First-line Treatment for Non-Small Cell Lung Cancer (KEYNOTE-782)

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2018-002598-22 |
| Trial protocol | HU ES |
| Global end of trial date | 05 November 2021 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 09 November 2022 |
| First version publication date | 09 November 2022 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | 3475-782 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|--------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03664024 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Merck: KEYNOTE-782 |

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 05 November 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 05 November 2021 |
| Global end of trial reached? | Yes |
| Global end of trial date | 05 November 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Participants with Stage IV nonsquamous non-small cell lung cancer (NSCLC) without prior systemic treatment will be treated with standard of care pembrolizumab combined with platinum-doublet chemotherapy for 4 cycles, then pembrolizumab plus pemetrexed maintenance for up to 31 additional cycles. The platinum doublet would be pemetrexed plus the investigator's choice of either cisplatin or carboplatin. The primary objective is to evaluate if total baseline tumor mutation burden (TMB) in cell-free circulating tumor deoxyribonucleic acid (ctDNA) is predictive of objective response per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) by the investigator by estimating the level of association.

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 | 30 October 2018 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------|
| Country: Number of subjects enrolled | Canada: 5 |
| Country: Number of subjects enrolled | Hungary: 35 |
| Country: Number of subjects enrolled | Israel: 15 |
| Country: Number of subjects enrolled | Spain: 58 |
| Country: Number of subjects enrolled | United States: 5 |
| Worldwide total number of subjects | 118 |
| EEA total number of subjects | 93 |

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) | 60 |
| From 65 to 84 years | 57 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were screened in 5 countries for this study.

Period 1

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

Arms

| | |
|------------------|--|
| Arm title | Pembrolizumab plus platinum-doublet chemotherapy |
|------------------|--|

Arm description:

Participants received pembrolizumab 200 mg intravenous (IV) infusion every 3 weeks (Q3W) on the first day of each 21-day cycle combined with a platinum-doublet of pemetrexed 500 mg/m² IV infusion plus investigators choice of either carboplatin AUC 5 mg/mL/m or cisplatin 75 mg/m² IV Q3W for up to 4 cycles, then pembrolizumab 200 mg plus pemetrexed 500 mg/m² IV infusion for up to 31 additional cycles up to ~2 years.

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Pembrolizumab |
| Investigational medicinal product code | |
| Other name | MK-3475 |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

200 mg, Day 1 of each 21-day cycle (Q3W)

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

Dosage and administration details:

500 mg/m² every 3 weeks

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

Dosage and administration details:

AUC 5 mg/mL/min, Day 1 of each 21-day cycle for 4 cycles (Cycles 1 – 4). Investigator's choice of either cisplatin or carboplatin.

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

Dosage and administration details:

75 mg/m², Day 1 of each 21-day cycle for 4 cycles (Cycles 1 – 4). Investigator's choice of either cisplatin or carboplatin.

| Number of subjects in period 1 | Pembrolizumab plus platinum-doublet chemotherapy |
|---------------------------------------|--|
| Started | 118 |
| Treated | 117 |
| Completed | 0 |
| Not completed | 118 |
| Consent withdrawn by subject | 2 |
| Death | 80 |
| Follow-up discontinued by sponsor | 34 |
| Lost to follow-up | 2 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Pembrolizumab plus platinum-doublet chemotherapy |
|-----------------------|--|

Reporting group description:

Participants received pembrolizumab 200 mg intravenous (IV) infusion every 3 weeks (Q3W) on the first day of each 21-day cycle combined with a platinum-doublet of pemetrexed 500 mg/m² IV infusion plus investigators choice of either carboplatin AUC 5 mg/mL/m or cisplatin 75 mg/m² IV Q3W for up to 4 cycles, then pembrolizumab 200 mg plus pemetrexed 500 mg/m² IV infusion for up to 31 additional cycles up to ~2 years.

| Reporting group values | Pembrolizumab plus platinum-doublet chemotherapy | Total | |
|--|--|-------|--|
| Number of subjects | 118 | 118 | |
| Age categorical | | | |
| Units: Participants | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 60 | 60 | |
| From 65-84 years | 57 | 57 | |
| 85 years and over | 1 | 1 | |
| Age Continuous | | | |
| Units: Years | | | |
| arithmetic mean | 64.5 | | |
| standard deviation | ± 9.1 | - | |
| Sex: Female, Male | | | |
| Units: Participants | | | |
| Female | 46 | 46 | |
| Male | 72 | 72 | |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 1 | 1 | |
| Asian | 1 | 1 | |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | |
| Black or African American | 2 | 2 | |
| White | 114 | 114 | |
| More than one race | 0 | 0 | |
| Unknown or Not Reported | 0 | 0 | |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 2 | 2 | |
| Not Hispanic or Latino | 116 | 116 | |
| Unknown or Not Reported | 0 | 0 | |

End points

End points reporting groups

| | |
|-----------------------|--|
| Reporting group title | Pembrolizumab plus platinum-doublet chemotherapy |
|-----------------------|--|

Reporting group description:

Participants received pembrolizumab 200 mg intravenous (IV) infusion every 3 weeks (Q3W) on the first day of each 21-day cycle combined with a platinum-doublet of pemetrexed 500 mg/m² IV infusion plus investigators choice of either carboplatin AUC 5 mg/mL/m or cisplatin 75 mg/m² IV Q3W for up to 4 cycles, then pembrolizumab 200 mg plus pemetrexed 500 mg/m² IV infusion for up to 31 additional cycles up to ~2 years.

| | |
|----------------------------|--|
| Subject analysis set title | Pembrolizumab plus platinum-doublet chemotherapy overall |
|----------------------------|--|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

Participants received pembrolizumab 200 mg intravenous (IV) infusion every 3 weeks (Q3W) on the first day of each 21-day cycle combined with a platinum-doublet of pemetrexed 500 mg/m² IV infusion plus investigators choice of either carboplatin AUC 5 mg/mL/m or cisplatin 75 mg/m² IV Q3W for up to 4 cycles, then pembrolizumab 200 mg plus pemetrexed 500 mg/m² IV infusion for up to 31 additional cycles up to ~2 years. This analysis set includes all responders and non-responders who received at least one dose of study intervention and had samples evaluable for ctDNA TMB analysis.

| | |
|----------------------------|--|
| Subject analysis set title | Pembrolizumab plus platinum-doublet chemotherapy responder |
|----------------------------|--|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

Participants received pembrolizumab 200 mg intravenous (IV) infusion every 3 weeks (Q3W) on the first day of each 21-day cycle combined with a platinum-doublet of pemetrexed 500 mg/m² IV infusion plus investigators choice of either carboplatin AUC 5 mg/mL/m or cisplatin 75 mg/m² IV Q3W for up to 4 cycles, then pembrolizumab 200 mg plus pemetrexed 500 mg/m² IV infusion for up to 31 additional cycles up to ~2 years. Participants in this analysis set were considered responders if they had a complete or partial response. This analysis set is a subset of the overall arm and includes only responders who received at least one dose of study intervention and had samples evaluable for ctDNA TMB analysis.

| | |
|----------------------------|--|
| Subject analysis set title | Pembrolizumab plus platinum-doublet chemotherapy non-responder |
|----------------------------|--|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

Participants received pembrolizumab 200 mg intravenous (IV) infusion every 3 weeks (Q3W) on the first day of each 21-day cycle combined with a platinum-doublet of pemetrexed 500 mg/m² IV infusion plus investigators choice of either carboplatin AUC 5 mg/mL/m or cisplatin 75 mg/m² IV Q3W for up to 4 cycles, then pembrolizumab 200 mg plus pemetrexed 500 mg/m² IV infusion for up to 31 additional cycles up to ~2 years. Participants were considered non-responders if they did not have complete or partial response. This analysis set is a subset of the overall arm and includes only non-responders who received at least one dose of study intervention and had samples evaluable for ctDNA TMB analysis.

Primary: Objective Response Rate

| | |
|-----------------|--|
| End point title | Objective Response Rate ^[1] |
|-----------------|--|

End point description:

Objective response rate is the proportion of participants who have a confirmed complete response (CR) or partial response (PR). Objective response rate is assessed by investigator review according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. The analysis population consisted of all participants who received at least one dose of study intervention. The percentage of participants with an ORR is presented.

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

End point timeframe:

Up to ~25 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned for this endpoint.

| End point values | Pembrolizumab plus platinum-doublet chemotherapy | | | |
|-----------------------------------|--|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 117 | | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 40.2 (31.2 to 49.6) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Tumor mutation burden (TMB) in cell-free circulating tumor deoxyribonucleic acid (ctDNA)

| | |
|-----------------|---|
| End point title | Tumor mutation burden (TMB) in cell-free circulating tumor deoxyribonucleic acid (ctDNA) ^[2] |
|-----------------|---|

End point description:

Cell-free ctDNA allows the exploration of tumor features from blood samples. TMB is a measure of mutational load in tumor cells and expressed as the number of somatic mutations per megabase (Mut/MB) of DNA. Participants with missing data are considered non-responders. The analysis population consisted of all participants who received at least one dose of study intervention and had samples evaluable for ctDNA TMB analysis. The mean TMB in cell-free ctDNA of participants is presented.

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

End point timeframe:

Baseline (Day 1)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned for this endpoint.

| End point values | Pembrolizumab plus platinum-doublet chemotherapy overall | Pembrolizumab plus platinum-doublet chemotherapy responder | Pembrolizumab plus platinum-doublet chemotherapy non-responder | |
|--------------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 101 | 42 | 59 | |
| Units: Mut/MB | | | | |
| arithmetic mean (standard deviation) | 9 (± 11.6) | 8 (± 8.3) | 10 (± 13.5) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

| | |
|-----------------|------------------|
| End point title | Overall Survival |
|-----------------|------------------|

End point description:

OS is defined as the time from the start of treatment to death due to any cause. The analysis population consisted of all participants who received at least one dose of study intervention. The Kaplan-Meier estimate of median PFS using the product-limit (Kaplan-Meier) method for censored data is presented.

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

End point timeframe:

Up to ~36 months

| | | | | |
|----------------------------------|--|--|--|--|
| End point values | Pembrolizumab plus platinum-doublet chemotherapy | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 117 | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 18.1 (13.5 to 25.6) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

| | |
|-----------------|---------------------------------|
| End point title | Progression Free Survival (PFS) |
|-----------------|---------------------------------|

End point description:

PFS is defined as the time from enrollment to the first documented disease progression or death due to any cause, whichever occurs first as assessed by investigator review according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1). The analysis population consisted of all participants who received at least one dose of study intervention. The Kaplan-Meier estimate of median PFS using the product-limit (Kaplan-Meier) method for censored data is presented.

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

End point timeframe:

Up to ~36 months

| | | | | |
|----------------------------------|--|--|--|--|
| End point values | Pembrolizumab plus platinum-doublet chemotherapy | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 117 | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 7.2 (5.6 to 9.8) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who experienced one or more adverse events (AEs)

| | |
|-----------------|---|
| End point title | Percentage of Participants who experienced one or more adverse events (AEs) |
|-----------------|---|

End point description:

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. The analysis population consisted of all participants who received at least one dose of study intervention. The percentage of participants who experienced an AE is presented.

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

End point timeframe:

Up to ~31 months

| | | | | |
|-----------------------------------|--|--|--|--|
| End point values | Pembrolizumab plus platinum-doublet chemotherapy | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 117 | | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 100.0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants discontinuing study intervention due to an AE.

| | |
|-----------------|---|
| End point title | Percentage of participants discontinuing study intervention due to an AE. |
|-----------------|---|

End point description:

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. The analysis population consisted of all participants who received at least one dose of study intervention. The percentage of participants who discontinued the study intervention due to an AE is presented.

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

End point timeframe:

Up to ~28 months

| | | | | |
|-----------------------------------|--|--|--|--|
| End point values | Pembrolizumab plus platinum- doublet chemotherapy | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 117 | | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 38.5 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For All-Cause Mortality: from allocation up to ~36 months. For AEs from start of treatment up to ~31 months.

Adverse event reporting additional description:

All-cause mortality: All allocated participants. AEs: All allocated participants who received at least 1 dose of study intervention. Per protocol, MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to study drug are excluded as AEs.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 24.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | Pembrolizumab + Pemetrexed + Platinum Agent |
|-----------------------|---|

Reporting group description: -

| Serious adverse events | Pembrolizumab + Pemetrexed + Platinum Agent | | |
|---|---|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 60 / 117 (51.28%) | | |
| number of deaths (all causes) | 80 | | |
| number of deaths resulting from adverse events | 8 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Prostate cancer | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 2 / 117 (1.71%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Death | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Pyrexia | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 2 / 117 (1.71%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 3 / 117 (2.56%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonitis | | | |
| subjects affected / exposed | 2 / 117 (1.71%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 2 / 2 | | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 117 (1.71%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 2 / 117 (1.71%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Psychiatric disorders | | | |

| | | | |
|---|-----------------|--|--|
| Confusional state | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Troponin increased | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Femur fracture | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract stoma complication | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tibia fracture | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Myocarditis | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiotoxicity | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Pericardial effusion | | | |
| subjects affected / exposed | 2 / 117 (1.71%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hydrocephalus | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dizziness | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cognitive disorder | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Seizure | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vertebrobasilar insufficiency | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 3 / 117 (2.56%) | | |
| occurrences causally related to treatment / all | 2 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancytopenia | | | |
| subjects affected / exposed | 3 / 117 (2.56%) | | |
| occurrences causally related to treatment / all | 3 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 117 (1.71%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Febrile neutropenia | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 5 / 117 (4.27%) | | |
| occurrences causally related to treatment / all | 5 / 5 | | |
| deaths causally related to treatment / all | 2 / 2 | | |
| Eye disorders | | | |
| Papilloedema | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 4 / 117 (3.42%) | | |
| occurrences causally related to treatment / all | 3 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haematemesis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Immune-mediated hepatitis | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Stevens-Johnson syndrome | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 2 / 117 (1.71%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tubulointerstitial nephritis | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocrine disorders | | | |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Fracture malunion | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bone pain | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pathological fracture | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 2 / 117 (1.71%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Device related bacteraemia | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gangrene | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemophilus infection | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Influenza | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lung abscess | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 11 / 117 (9.40%) | | |
| occurrences causally related to treatment / all | 3 / 13 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Pulmonary sepsis | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 4 / 117 (3.42%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 117 (1.71%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 117 (1.71%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 2 / 117 (1.71%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 117 (0.85%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Pembrolizumab + Pemetrexed + Platinum Agent | | |
|---|---|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 114 / 117 (97.44%) | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 30 / 117 (25.64%) | | |
| occurrences (all) | 46 | | |
| Chest pain | | | |
| subjects affected / exposed | 7 / 117 (5.98%) | | |
| occurrences (all) | 9 | | |
| Fatigue | | | |
| subjects affected / exposed | 25 / 117 (21.37%) | | |
| occurrences (all) | 39 | | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 10 / 117 (8.55%) | | |
| occurrences (all) | 10 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 16 / 117 (13.68%) | | |
| occurrences (all) | 19 | | |
| Pyrexia | | | |
| subjects affected / exposed | 16 / 117 (13.68%) | | |
| occurrences (all) | 25 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 12 / 117 (10.26%) | | |
| occurrences (all) | 13 | | |
| Pneumonitis | | | |

| | | | |
|--------------------------------------|-------------------|--|--|
| subjects affected / exposed | 7 / 117 (5.98%) | | |
| occurrences (all) | 8 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 17 / 117 (14.53%) | | |
| occurrences (all) | 20 | | |
| Investigations | | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 18 / 117 (15.38%) | | |
| occurrences (all) | 33 | | |
| Amylase increased | | | |
| subjects affected / exposed | 9 / 117 (7.69%) | | |
| occurrences (all) | 14 | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 20 / 117 (17.09%) | | |
| occurrences (all) | 32 | | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 6 / 117 (5.13%) | | |
| occurrences (all) | 7 | | |
| Weight decreased | | | |
| subjects affected / exposed | 14 / 117 (11.97%) | | |
| occurrences (all) | 14 | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 7 / 117 (5.98%) | | |
| occurrences (all) | 8 | | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 8 / 117 (6.84%) | | |
| occurrences (all) | 10 | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 17 / 117 (14.53%) | | |
| occurrences (all) | 30 | | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 10 / 117 (8.55%) | | |
| occurrences (all) | 10 | | |
| Dysgeusia | | | |

| | | | |
|---|--------------------------|--|--|
| subjects affected / exposed occurrences (all) | 7 / 117 (5.98%) 7 | | |
| Headache subjects affected / exposed occurrences (all) | 9 / 117 (7.69%) 10 | | |
| Neuropathy peripheral subjects affected / exposed occurrences (all) | 7 / 117 (5.98%) 7 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 72 / 117 (61.54%) 109 | | |
| Leukopenia subjects affected / exposed occurrences (all) | 13 / 117 (11.11%) 16 | | |
| Neutropenia subjects affected / exposed occurrences (all) | 29 / 117 (24.79%) 50 | | |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 17 / 117 (14.53%) 23 | | |
| Eye disorders | | | |
| Lacrimation increased subjects affected / exposed occurrences (all) | 14 / 117 (11.97%) 14 | | |
| Gastrointestinal disorders | | | |
| Constipation subjects affected / exposed occurrences (all) | 21 / 117 (17.95%) 24 | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 27 / 117 (23.08%) 44 | | |
| Nausea subjects affected / exposed occurrences (all) | 36 / 117 (30.77%) 44 | | |
| Vomiting | | | |

| | | | |
|--|-------------------------|--|--|
| subjects affected / exposed occurrences (all) | 22 / 117 (18.80%) 27 | | |
| Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) | 6 / 117 (5.13%) 8 | | |
| Rash subjects affected / exposed occurrences (all) | 7 / 117 (5.98%) 13 | | |
| Renal and urinary disorders Renal impairment subjects affected / exposed occurrences (all) | 9 / 117 (7.69%) 10 | | |
| Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all) | 14 / 117 (11.97%) 17 | | |
| Hyperthyroidism subjects affected / exposed occurrences (all) | 7 / 117 (5.98%) 8 | | |
| Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all) | 6 / 117 (5.13%) 8 | | |
| Arthralgia subjects affected / exposed occurrences (all) | 16 / 117 (13.68%) 22 | | |
| Back pain subjects affected / exposed occurrences (all) | 12 / 117 (10.26%) 13 | | |
| Infections and infestations Pneumonia subjects affected / exposed occurrences (all) | 7 / 117 (5.98%) 7 | | |
| Urinary tract infection | | | |

| | | | |
|------------------------------------|-------------------|--|--|
| subjects affected / exposed | 13 / 117 (11.11%) | | |
| occurrences (all) | 19 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 25 / 117 (21.37%) | | |
| occurrences (all) | 26 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 21 / 117 (17.95%) | | |
| occurrences (all) | 25 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 8 / 117 (6.84%) | | |
| occurrences (all) | 9 | | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 6 / 117 (5.13%) | | |
| occurrences (all) | 7 | | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 6 / 117 (5.13%) | | |
| occurrences (all) | 9 | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 9 / 117 (7.69%) | | |
| occurrences (all) | 10 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 15 May 2019 | Amendment one includes direction for re-consenting participants upon disease progression, moving the collection time point of one of the primary endpoint samples, and correcting errors in the Schedule of Activities. |
| 30 September 2021 | Amendment two includes instruction that allows participants to be enrolled in a pembrolizumab extension study upon study completion, add final analysis in the statistical analysis plan, and update the Sponsor's branding information. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported