# Clinical trial results:
# A Phase III, Randomized, Open-label Clinical trial of Pembrolizumab (MK-3475) versus Paclitaxel in Subjects with Advanced Gastric or Gastroesophageal Junction Adenocarcinoma who Progressed after First-line Therapy with Platinum and Fluoropyrimidine

## Summary

| | |
|---|---|
| EudraCT number | 2014-005241-45 |
| Trial protocol | FI IT EE ES IE DE GB DK BE PL |
| Global end of trial date | 10 June 2021 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 25 June 2022 |
| First version publication date | 25 June 2022 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | 3475-061 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02370498 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | JAPIC: 152988 |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Merck Sharp & Dohme LLC |
| Sponsor organisation address | 126 East Lincoln Avenue, P.O. Box 2000, Rahway, NJ, United States, 07065 |
| Public contact | Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.com |
| Scientific contact | Clinical Trials Disclosure, Merck Sharp & 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 | 10 June 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 26 October 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 10 June 2021 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

This is a study for participants with advanced gastric or gastroesophageal junction adenocarcinoma who have had tumor progression after first-line treatment with platinum and fluoropyrimidine doublet therapy. The primary study hypotheses are that pembrolizumab (MK-3475) prolongs progression free survival (PFS) and overall survival (OS) for participants with tumors that show positive programmed cell death ligand 1 (PD-L1) expression. As of 20-March-2016, enrollment will be limited to PD-L1 positive participants.

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 | 11 May 2015 |
| 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: 17 |
| Country: Number of subjects enrolled | Belgium: 8 |
| Country: Number of subjects enrolled | Canada: 4 |
| Country: Number of subjects enrolled | Chile: 17 |
| Country: Number of subjects enrolled | Colombia: 4 |
| Country: Number of subjects enrolled | Denmark: 13 |
| Country: Number of subjects enrolled | Estonia: 11 |
| Country: Number of subjects enrolled | Finland: 2 |
| Country: Number of subjects enrolled | Germany: 40 |
| Country: Number of subjects enrolled | Guatemala: 10 |
| Country: Number of subjects enrolled | Ireland: 19 |
| Country: Number of subjects enrolled | Israel: 26 |
| Country: Number of subjects enrolled | Italy: 59 |
| Country: Number of subjects enrolled | Japan: 100 |
| Country: Number of subjects enrolled | Korea, Republic of: 47 |
| Country: Number of subjects enrolled | Malaysia: 2 |
| Country: Number of subjects enrolled | Mexico: 2 |

| | |
|---|---|
| Country: Number of subjects enrolled | New Zealand: 1 |
| Country: Number of subjects enrolled | Norway: 13 |
| Country: Number of subjects enrolled | Poland: 17 |
| Country: Number of subjects enrolled | Russian Federation: 37 |
| Country: Number of subjects enrolled | Singapore: 9 |
| Country: Number of subjects enrolled | South Africa: 2 |
| Country: Number of subjects enrolled | Spain: 31 |
| Country: Number of subjects enrolled | Taiwan: 18 |
| Country: Number of subjects enrolled | Turkey: 19 |
| Country: Number of subjects enrolled | United Kingdom: 30 |
| Country: Number of subjects enrolled | United States: 30 |
| Country: Number of subjects enrolled | Argentina: 3 |
| Country: Number of subjects enrolled | Hong Kong: 1 |
| Worldwide total number of subjects | 592 |
| EEA total number of subjects | 213 |

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) | 353 |
| From 65 to 84 years | 237 |
| 85 years and over | 2 |

## Subject disposition

### Recruitment

Recruitment details:

After 20 March 2016, enrollment was limited to programmed cell death ligand 1 (PD-L1) positive participants.

### Pre-assignment

Screening details:

Of 592 participants that were randomized to trial, 570 received treatment. At the time of the primary analysis data cut-off, 89 participants were ongoing in the study.

### Period 1

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

### Arms

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

Arm description:

Participants receive 200 mg intravenous (IV) pembrolizumab on Day 1 of each 21-day cycle, for up to 35 administrations (approximately 2 years).

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

Dosage and administration details:

200 mg IV Day 1 of each 3-week cycle

| | |
|---|---|
| **Arm title** | Paclitaxel |

Arm description:

Participants receive paclitaxel 80 mg/m^2 IV, on Days 1, 8, and 15 of each 28-day cycle until disease progression or unacceptable toxicity.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Paclitaxel |
| Investigational medicinal product code | |
| Other name | TAXOL® |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

80 mg/m^2 on Days 1, 8, and 15 of each 4-week cycle

| **Number of subjects in period 1** | Pembrolizumab | Paclitaxel |
|---|---|---|
| Started | 296 | 296 |
| Treated | 294 | 276 |
| PD-L1 Positive Participants | 196 | 199 |
| Completed | 0 | 0 |
| Not completed | 296 | 296 |
| Adverse event, serious fatal | 10 | 8 |
| Sponsor's decision | 15 | 9 |
| Consent withdrawn by subject | 7 | 12 |
| Death | 263 | 265 |
| Protocol deviation | 1 | 2 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Pembrolizumab |
| Reporting group description: | |
| Participants receive 200 mg intravenous (IV) pembrolizumab on Day 1 of each 21-day cycle, for up to 35 administrations (approximately 2 years). | |
| Reporting group title | Paclitaxel |
| Reporting group description: | |
| Participants receive paclitaxel 80 mg/m^2 IV, on Days 1, 8, and 15 of each 28-day cycle until disease progression or unacceptable toxicity. | |

| Reporting group values | Pembrolizumab | Paclitaxel | Total |
|---|---|---|---|
| Number of subjects | 296 | 296 | 592 |
| Age categorical<br>Units: Participants | | | |
| Adults (18-64 years) | 170 | 183 | 353 |
| From 65-84 years | 125 | 112 | 237 |
| 85 years and over | 1 | 1 | 2 |
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | 60.7 | 59.6 | |
| standard deviation | ± 12.0 | ± 11.7 | - |
| Sex: Female, Male<br>Units: Participants | | | |
| Female | 94 | 88 | 182 |
| Male | 202 | 208 | 410 |
| Race (NIH/OMB)<br>Units: Subjects | | | |
| American Indian or Alaska Native | 4 | 3 | 7 |
| Asian | 93 | 91 | 184 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 4 | 2 | 6 |
| White | 193 | 198 | 391 |
| More than one race | 2 | 2 | 4 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 27 | 24 | 51 |
| Not Hispanic or Latino | 269 | 272 | 541 |
| Unknown or Not Reported | 0 | 0 | 0 |
| PD-L1 Status<br>Units: Subjects | | | |
| Positive | 196 | 199 | 395 |
| Negative | 99 | 96 | 195 |
| Unknown | 1 | 1 | 2 |
| Region of Enrollment<br>Units: Subjects | | | |

| | | | |
|---|---|---|---|
| Europe/Israel/North America/Australia | 190 | 187 | 377 |
| Asia | 88 | 89 | 177 |
| Rest of World | 18 | 20 | 38 |
| Time To Progression (TTP) on first-line therapy<br>Units: Subjects | | | |
| <6 months | 186 | 182 | 368 |
| ≥6 months | 110 | 114 | 224 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Pembrolizumab |
| Reporting group description: | |
| Participants receive 200 mg intravenous (IV) pembrolizumab on Day 1 of each 21-day cycle, for up to 35 administrations (approximately 2 years). | |
| Reporting group title | Paclitaxel |
| Reporting group description: | |
| Participants receive paclitaxel 80 mg/m^2 IV, on Days 1, 8, and 15 of each 28-day cycle until disease progression or unacceptable toxicity. | |

### Primary: Progression-free Survival (PFS) According to Response Criteria in Solid Tumors Version 1.1 (RECIST 1.1) Based on Blinded Independent Central Review (BICR) in Programmed Death-Ligand 1 (PD-L1) Positive Participants

| | |
|---|---|
| End point title | Progression-free Survival (PFS) According to Response Criteria in Solid Tumors Version 1.1 (RECIST 1.1) Based on Blinded Independent Central Review (BICR) in Programmed Death-Ligand 1 (PD-L1) Positive Participants |
| End point description: | |
| PFS was defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on BICR, or death due to any cause, whichever occurs first. According to RECIST 1.1, progressive disease (PD) was defined as a 20% relative increase in the sum of diameters (SOD) of target lesions, taking as reference the nadir SOD and an absolute increase of >5 mm in the SOD, or the appearance of new lesions. PFS was analyzed using the Kaplan-Meier method and median PFS (95% confidence interval [CI]) in months was reported for PD-L1 positive participants by treatment group. All randomized PD-L1 positive participants were analyzed. Participants were included in the treatment group to which they were randomized. | |
| End point type | Primary |
| End point timeframe: | |
| Up to 30 months (through database cut-off date of 26 Oct 2017) | |

| **End point values** | Pembrolizumab | Paclitaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 196 | 199 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 1.5 (1.4 to 2.0) | 4.1 (3.1 to 4.2) | | |

### Statistical analyses

| | |
|---|---|
| **Statistical analysis title** | PFS per RECIST 1.1 - PD-L1 positive participants |
| Statistical analysis description: | |
| Treatment difference in PFS was assessed by the Stratified Log-rank test, and a stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (Hazard Ratio [HR]) between the treatment arms. | |
| Comparison groups | Paclitaxel v Pembrolizumab |

| | |
|---|---|
| Number of subjects included in analysis | 395 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.98358 [1] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.27 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.03 |
| upper limit | 1.57 |

Notes:

[1] - One-sided p-value based on log-rank test stratified by geographic region (Europe/Israel/North America/Australia vs. Asia vs. Rest of World) and TTP on first-line therapy (< 6 months vs. >= 6 months).

## Primary: Overall Survival (OS) in PD-L1 Positive Participants

| | |
|---|---|
| End point title | Overall Survival (OS) in PD-L1 Positive Participants |

End point description:

OS was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the final analysis were censored at the date of the last follow-up. OS was analyzed using the Kaplan-Meier method and median OS (95% CI) in months was reported for PD-L1 positive participants by treatment group. All randomized PD-L1 positive participants were analyzed. Participants were included in the treatment group to which they were randomized.

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

End point timeframe:

Up to 30 months (through database cut-off date of 26 Oct 2017)

| **End point values** | Pembrolizumab | Paclitaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 196 | 199 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 9.1 (6.2 to 10.7) | 8.3 (7.6 to 9.0) | | |

### Statistical analyses

| **Statistical analysis title** | OS - PD-L1 positive participants |
|---|---|

Statistical analysis description:

Treatment difference in OS was assessed by the Stratified Log-rank test, and a stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (HR) between the treatment arms.

| | |
|---|---|
| Comparison groups | Pembrolizumab v Paclitaxel |

| | |
|---|---|
| Number of subjects included in analysis | 395 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.04205 [2] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.82 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.66 |
| upper limit | 1.03 |

Notes:

[2] - One-sided p-value based on log-rank test stratified by geographic region (Europe/Israel/North America/Australia vs. Asia vs. Rest of World) and TTP on first-line therapy (< 6 months vs. >= 6 months).

## Secondary: PFS According to RECIST 1.1 Based on BICR in All Participants

| | |
|---|---|
| End point title | PFS According to RECIST 1.1 Based on BICR in All Participants |

End point description:

PFS was defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on BICR, or death due to any cause, whichever occurs first. According to RECIST 1.1, PD was defined as a 20% relative increase in the SOD of target lesions, taking as reference the nadir SOD and an absolute increase of >5 mm in the SOD, or the appearance of new lesions. PFS was analyzed using the Kaplan-Meier method and median PFS (95% CI) in months was reported for all participants by treatment group. All randomized participants were analyzed. Participants were included in the treatment group to which they were randomized.

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

End point timeframe:

Up to 30 months (through database cut-off date of 26 Oct 2017)

| **End point values** | Pembrolizumab | Paclitaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 296 | 296 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 1.5 (1.4 to 1.6) | 4.1 (3.2 to 4.2) | | |

### Statistical analyses

| **Statistical analysis title** | PFS per RECIST 1.1 - all participants |
|---|---|

Statistical analysis description:

Treatment difference in PFS was assessed by the Stratified Log-rank test, and a stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (Hazard Ratio [HR]) between the treatment arms.

| | |
|---|---|
| Comparison groups | Pembrolizumab v Paclitaxel |

| | |
|---|---|
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.99999 [3] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.49 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.25 |
| upper limit | 1.77 |

Notes:

[3] - One-sided p-value based on log-rank test stratified by geographic region (Europe/Israel/North America/Australia vs. Asia vs. Rest of World), TTP on first-line therapy (< 6 months vs. >= 6 months), and PD-L1 status (positive vs. negative).

## Secondary: OS in All Participants

| | |
|---|---|
| End point title | OS in All Participants |

End point description:

OS was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the final analysis were censored at the date of the last follow-up. OS was analyzed using the Kaplan-Meier method and median OS (95% CI) in months was reported for all participants by treatment group. All randomized participants were analyzed. Participants were included in the treatment group to which they were randomized.

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

End point timeframe:

Up to 30 months (through database cut-off date of 26 Oct 2017)

| **End point values** | Pembrolizumab | Paclitaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 296 | 296 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 6.7 (5.4 to 8.9) | 8.3 (7.7 to 8.8) | | |

### Statistical analyses

| **Statistical analysis title** | OS - all participants |
|---|---|

Statistical analysis description:

Treatment difference in OS was assessed by the Stratified Log-rank test, and a stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (Hazard Ratio [HR]) between the treatment arms.

| | |
|---|---|
| Comparison groups | Pembrolizumab v Paclitaxel |

| | |
|---|---|
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.24463 [4] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.94 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.79 |
| upper limit | 1.12 |

Notes:

[4] - One-sided p-value based on log-rank test stratified by geographic region (Europe/Israel/North America/Australia vs. Asia vs. Rest of World), TTP on first-line therapy (<6 months vs. ≥6 months), and PD-L1 status (positive vs. negative).

## Secondary: PFS According to RECIST 1.1 Based on Investigator Assessment in PD-L1 Positive Participants

| | |
|---|---|
| End point title | PFS According to RECIST 1.1 Based on Investigator Assessment in PD-L1 Positive Participants |

End point description:

PFS was defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on investigator assessment, or death due to any cause, whichever occurs first. According to RECIST 1.1, PD was defined as a 20% relative increase in the SOD of target lesions, taking as reference the nadir SOD and an absolute increase of >5 mm in the SOD, or the appearance of new lesions. PFS was analyzed using the Kaplan-Meier method and median PFS (95% CI) in months was reported for PD-L1 positive participants by treatment group. All randomized PD-L1 positive participants were analyzed. Participants were included in the treatment group to which they were randomized.

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

End point timeframe:

Up to 30 months (through database cut-off date of 26 Oct 2017)

| **End point values** | Pembrolizumab | Paclitaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 196 | 199 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 1.6 (1.5 to 2.7) | 3.1 (2.8 to 4.0) | | |

### Statistical analyses

| **Statistical analysis title** | PFS per RECIST 1.1 - PD-L1 positive participants |
|---|---|

Statistical analysis description:

Treatment difference in PFS was assessed by the Stratified Log-rank test, and a stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (HR) between the treatment arms.

| | |
|---|---|
| Comparison groups | Pembrolizumab v Paclitaxel |

| | |
|---|---|
| Number of subjects included in analysis | 395 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.41331 [5] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.98 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.79 |
| upper limit | 1.21 |

Notes:

[5] - One-sided p-value based on log-rank test stratified by geographic region (Europe/Israel/North America/Australia vs. Asia vs. Rest of World) and TTP on first-line therapy (<6 months vs. ≥6 months).

## Secondary: PFS According to RECIST 1.1 Based on Investigator Assessment in All Participants

| | |
|---|---|
| End point title | PFS According to RECIST 1.1 Based on Investigator Assessment in All Participants |

End point description:

PFS was defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on investigator assessment, or death due to any cause, whichever occurs first. According to RECIST 1.1, PD was defined as a 20% relative increase in the SOD of target lesions, taking as reference the nadir SOD and an absolute increase of >5 mm in the SOD, or the appearance of new lesions. PFS was analyzed using the Kaplan-Meier method and median PFS (95% CI) in months was reported for all participants by treatment group. All randomized participants were analyzed. Participants were included in the treatment group to which they were randomized.

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

End point timeframe:

Up to 30 months (through database cut-off date of 26 Oct 2017)

| **End point values** | Pembrolizumab | Paclitaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 296 | 296 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 1.6 (1.5 to 1.9) | 3.2 (2.9 to 4.0) | | |

### Statistical analyses

| **Statistical analysis title** | PFS per RECIST 1.1 - all participants |
|---|---|

Statistical analysis description:

Treatment difference in PFS was assessed by the Stratified Log-rank test, and a stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (HR) between the treatment arms.

| | |
|---|---|
| Comparison groups | Pembrolizumab v Paclitaxel |

| | |
|---|---|
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.97481 [6] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1 |
| upper limit | 1.42 |

Notes:

[6] - One-sided p-value based on log-rank test stratified by geographic region (Europe/Israel/North America/Australia vs. Asia vs. Rest of World), TTP on first-line therapy (<6 months vs. ≥6 months), and PD-L1 status (positive vs. negative).

## Secondary: PFS According to Immune-Related Response Evaluation Criteria in Solid Tumors (irRECIST) Based on BICR in PD-L1 Positive Participants

| | |
|---|---|
| End point title | PFS According to Immune-Related Response Evaluation Criteria in Solid Tumors (irRECIST) Based on BICR in PD-L1 Positive Participants |

End point description:

PFS defined as time from randomization to first documented PD per irRECIST based on BICR, or death due to any cause, whichever occurs first. Following initial PD by RECIST 1.1 (20% relative increase in SOD of target lesions), participants were assessed according to irRECIST: tumor assessment repeated ≥4 weeks later to confirm PD with option of continuing treatment until scan was obtained for clinically stable participants. If PD confirmed, participant was discontinued from treatment unless investigator found benefit. If repeat scan showed stable disease (SD; neither sufficient shrinkage or increase of lesion), partial response (PR; ≥30% decrease in SOD of lesions), or complete response (CR; disappearance of all non-nodal lesions), participant could continue treatment at investigator's discretion. PFS using Kaplan-Meier and median PFS (95% CI) in months was reported. All randomized PD-L1 positive participants were analyzed and included in treatment group to which they were randomized.

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

End point timeframe:

Up to 30 months (through database cut-off date of 26 Oct 2017)

| **End point values** | Pembrolizumab | Paclitaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 196 | 199 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 1.9 (1.4 to 3.0) | 4.2 (3.5 to 4.4) | | |

### Statistical analyses

| **Statistical analysis title** | PFS per irRECIST - PD-L1 positive participants |
|---|---|

Statistical analysis description:

Treatment difference in PFS was assessed by the Stratified Log-rank test, and a stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (HR) between the treatment arms.

| | |
|---|---|
| Comparison groups | Pembrolizumab v Paclitaxel |

| | |
|---|---|
| Number of subjects included in analysis | 395 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.80696 [7] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.89 |
| upper limit | 1.38 |

Notes:

[7] - One-sided p-value based on log-rank test stratified by geographic region (Europe/Israel/North America/Australia vs. Asia vs. Rest of World) and TTP on first-line therapy (<6 months vs. ≥6 months).

## Secondary: PFS According to irRECIST Based on BICR in All Participants

| | |
|---|---|
| End point title | PFS According to irRECIST Based on BICR in All Participants |

End point description:

PFS defined as time from randomization to first documented PD per irRECIST based on BICR, or death due to any cause, whichever occurs first. Following initial PD by RECIST 1.1 (20% relative increase in SOD of target lesions), participants were assessed according to irRECIST: tumor assessment was repeated ≥4 weeks later to confirm PD with option of continuing treatment until this scan was obtained for clinically stable participants. If PD confirmed, participant was discontinued from treatment unless investigator determined benefit. If repeat scan indicated SD (neither sufficient shrinkage or increase of target lesion), PR (≥30% decrease in the SOD of target lesions), or CR (disappearance of all non-nodal target lesions), participant could continue treatment at investigator's discretion. PFS analyzed using Kaplan-Meier method and median PFS (95% CI) in months was reported. All randomized participants were analyzed and included in the treatment group to which they were randomized.

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

End point timeframe:

Up to 30 months (through database cut-off date of 26 Oct 2017)

| **End point values** | Pembrolizumab | Paclitaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 296 | 296 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 1.6 (1.5 to 2.5) | 4.2 (4.0 to 4.4) | | |

### Statistical analyses

| **Statistical analysis title** | PFS per irRECIST - all participants |
|---|---|

Statistical analysis description:

Treatment difference in PFS was assessed by the Stratified Log-rank test, and a stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (HR) between the treatment arms.

| | |
|---|---|
| Comparison groups | Pembrolizumab v Paclitaxel |

| | |
|---|---|
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.99932 [8] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.34 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.12 |
| upper limit | 1.6 |

Notes:

[8] - One-sided p-value based on log-rank test stratified by geographic region (Europe/Israel/North America/Australia vs. Asia vs. Rest of World), TTP on first-line therapy (< 6 months vs. >= 6 months), and PD-L1 status (positive vs. negative).

## Secondary: Time to Tumor Progression (TTP) According to RECIST 1.1 Based on BICR in PD-L1 Positive Participants

| | |
|---|---|
| End point title | Time to Tumor Progression (TTP) According to RECIST 1.1 Based on BICR in PD-L1 Positive Participants |

End point description:

TTP was defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on BICR. Using RECIST 1.1, progressive disease was defined as a 20% relative increase in the SOD of target lesions, taking as reference the nadir SOD and an absolute increase of >5 mm in the SOD, or the appearance of new lesions. If there was no documented disease progression, TTP was censored at last tumor assessment date. TTP was analyzed using the Kaplan-Meier method and median TTP (95% CI) in months was reported for PD-L1 positive participants by treatment group. All randomized PD-L1 positive participants were analyzed. Participants were included in the treatment group to which they were randomized.

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

End point timeframe:

Up to 30 months (through database cut-off date of 26 Oct 2017)

| **End point values** | Pembrolizumab | Paclitaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 196 | 199 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 1.6 (1.4 to 2.7) | 4.0 (3.1 to 4.2) | | |

### Statistical analyses

| **Statistical analysis title** | TTP per RECIST 1.1 - PD-L1 positive participants |
|---|---|

Statistical analysis description:

Treatment difference in TTP was assessed by the Stratified Log-rank test, and a stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (HR) between the treatment arms.

| | |
|---|---|
| Comparison groups | Pembrolizumab v Paclitaxel |

| | |
|---|---|
| Number of subjects included in analysis | 395 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.99661 [9] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.45 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.11 |
| upper limit | 1.89 |

Notes:

[9] - One-sided p-value based on log-rank test stratified by geographic region (Europe/Israel/North America/Australia vs. Asia vs. Rest of World) and TTP on first-line therapy (<6 months vs. ≥6 months).

## Secondary: TTP According to RECIST 1.1 Based on BICR in All Participants

| | |
|---|---|
| End point title | TTP According to RECIST 1.1 Based on BICR in All Participants |

End point description:

TTP was defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on BICR. Using RECIST 1.1, progressive disease was defined as a 20% relative increase in the SOD of target lesions, taking as reference the nadir SOD and an absolute increase of >5 mm in the SOD, or the appearance of new lesions. If there was no documented disease progression, TTP was censored at last tumor assessment date. TTP was analyzed using the Kaplan-Meier method and median TTP (95% CI) in months was reported for all participants by treatment group. All randomized participants were analyzed. Participants were included in the treatment group to which they were randomized.

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

End point timeframe:

Up to 30 months (through database cut-off date of 26 Oct 2017)

| **End point values** | Pembrolizumab | Paclitaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 296 | 296 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 1.5 (1.4 to 1.8) | 4.1 (3.2 to 4.2) | | |

### Statistical analyses

| **Statistical analysis title** | TTP per RECIST 1.1 - all participants |
|---|---|

Statistical analysis description:

Treatment difference in TTP was assessed by the Stratified Log-rank test, and a stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (HR) between the treatment arms.

| | |
|---|---|
| Comparison groups | Pembrolizumab v Paclitaxel |

| | |
|---|---|
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 1 [10] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.77 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.42 |
| upper limit | 2.2 |

Notes:

[10] - One-sided p-value based on log-rank test stratified by geographic region (Europe/Israel/North America/Australia vs. Asia vs. Rest of World), TTP on first-line therapy (< 6 months vs. >= 6 months), and PD-L1 status (positive vs. negative).

## Secondary: TTP According to RECIST 1.1 Based on Investigator Assessment in PD-L1 Positive Participants

| | |
|---|---|
| End point title | TTP According to RECIST 1.1 Based on Investigator Assessment in PD-L1 Positive Participants |

End point description:

TTP was defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on investigator assessment. Using RECIST 1.1, progressive disease was defined as a 20% relative increase in the SOD of target lesions, taking as reference the nadir SOD and an absolute increase of >5 mm in the SOD, or the appearance of new lesions. If there was no documented disease progression, TTP was censored at last tumor assessment date. TTP was analyzed using the Kaplan-Meier method and median TTP (95% CI) in months was reported for PD-L1 positive participants by treatment group. All randomized PD-L1 positive participants were analyzed. Participants were included in the treatment group to which they were randomized.

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

End point timeframe:

Up to 30 months (through database cut-off date of 26 Oct 2017)

| **End point values** | Pembrolizumab | Paclitaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 196 | 199 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 2.1 (1.5 to 3.0) | 3.3 (2.9 to 4.1) | | |

### Statistical analyses

| **Statistical analysis title** | TTP per RECIST 1.1 - all participants |
|---|---|

Statistical analysis description:

Treatment difference in TTP was assessed by the Stratified Log-rank test, and a stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (HR) between the treatment arms.

| | |
|---|---|
| Comparison groups | Pembrolizumab v Paclitaxel |

| | |
|---|---|
| Number of subjects included in analysis | 395 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.3928 [11] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.97 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.77 |
| upper limit | 1.23 |

Notes:

[11] - One-sided p-value based on log-rank test stratified by geographic region (Europe/Israel/North America/Australia vs. Asia vs. Rest of World) and TTP on first-line therapy (<6 months vs. ≥6 months).

## Secondary: TTP According to RECIST 1.1 Based on Investigator Assessment in All Participants

| | |
|---|---|
| End point title | TTP According to RECIST 1.1 Based on Investigator Assessment in All Participants |

End point description:

TTP was defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on investigator assessment. Using RECIST 1.1, progressive disease was defined as a 20% relative increase in the SOD of target lesions, taking as reference the nadir SOD and an absolute increase of >5 mm in the SOD, or the appearance of new lesions. If there was no documented disease progression, TTP was censored at last tumor assessment date. TTP was analyzed using the Kaplan-Meier method and median TTP (95% CI) in months was reported for all participants by treatment group. All randomized participants were analyzed. Participants were included in the treatment group to which they were randomized.

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

End point timeframe:

Up to 30 months (through database cut-off date of 26 Oct 2017)

| **End point values** | Pembrolizumab | Paclitaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 296 | 296 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 1.6 (1.5 to 2.7) | 3.8 (3.0 to 4.1) | | |

## Statistical analyses

| **Statistical analysis title** | TTP per RECIST 1.1 - all participants |
|---|---|

Statistical analysis description:

Treatment difference in TTP was assessed by the Stratified Log-rank test, and a stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (HR) between the treatment arms.

| | |
|---|---|
| Comparison groups | Pembrolizumab v Paclitaxel |

| | |
|---|---|
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.97033 [12] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1 |
| upper limit | 1.47 |

Notes:

[12] - One-sided p-value based on log-rank test stratified by geographic region (Europe/Israel/North America/Australia vs. Asia vs. Rest of World), TTP on first-line therapy (< 6 months vs. >= 6 months), and PD-L1 status (positive vs. negative).

## Secondary: Objective Response Rate (ORR) According to RECIST 1.1 Based on BICR in PD-L1 Positive Participants

| | |
|---|---|
| End point title | Objective Response Rate (ORR) According to RECIST 1.1 Based on BICR in PD-L1 Positive Participants |

End point description:

ORR was defined as the percentage of the participants in the analysis population who had a confirmed CR (disappearance of all non-nodal target lesions and any pathological lymph nodes must have become normal) or PR (at least a 30% decrease in the SOD of target lesions, taking as reference the baseline SOD) according to RECIST 1.1 and based on BICR. ORR was analyzed using the stratified Miettinen and Nurminen method, and reported with 95% CI for PD-L1 positive participants by treatment group. All randomized PD-L1 positive participants were analyzed. Participants were included in the treatment group to which they were randomized.

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

End point timeframe:

Up to 30 months (through database cut-off date of 26 Oct 2017)

| **End point values** | Pembrolizumab | Paclitaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 196 | 199 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 15.8 (11.0 to 21.7) | 13.6 (9.1 to 19.1) | | |

### Statistical analyses

| **Statistical analysis title** | ORR per RECIST 1.1 - PD-L1 positive participants |
|---|---|

Statistical analysis description:

Stratified Miettinen and Nurminen's (MN) method was used for comparison of the ORR between the treatment arms. A 95% CI for the difference in response rates between the pembrolizumab arm and paclitaxel arm was provided.

| | |
|---|---|
| Comparison groups | Pembrolizumab v Paclitaxel |

| | |
|---|---|
| Number of subjects included in analysis | 395 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.28967 [13] |
| Method | Miettinen and Nurminen method |
| Parameter estimate | Difference in Percentage |
| Point estimate | 2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5 |
| upper limit | 9.1 |

Notes:

[13] - Stratification factors for MN method included geographic region (Europe/Israel/North America/Australia vs. Asia vs. Rest of World) and TTP on first-line therapy (<6 months vs. ≥6 months) weighting by sample size.

## Secondary: ORR According to RECIST 1.1 Based on BICR in All Participants

| | |
|---|---|
| End point title | ORR According to RECIST 1.1 Based on BICR in All Participants |

End point description:

ORR was defined as the percentage of the participants in the analysis population who had a confirmed CR (disappearance of all non-nodal target lesions and any pathological lymph nodes must have become normal) or PR (at least a 30% decrease in the SOD of target lesions, taking as reference the baseline SOD) according to RECIST 1.1 and based on BICR. ORR was analyzed using the stratified Miettinen and Nurminen method, and reported with 95% CI for all participants by treatment group. All randomized participants were analyzed. Participants were included in the treatment group to which they were randomized.

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

End point timeframe:

Up to 30 months (through database cut-off date of 26 Oct 2017)

| **End point values** | Pembrolizumab | Paclitaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 296 | 296 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 11.1 (7.8 to 15.3) | 12.5 (9.0 to 16.8) | | |

### Statistical analyses

| **Statistical analysis title** | ORR per RECIST 1.1 - all participants |
|---|---|

Statistical analysis description:

Stratified MN method was used for comparison of the ORR between the treatment arms. A 95% CI for the difference in response rates between the pembrolizumab arm and paclitaxel arm was provided.

| | |
|---|---|
| Comparison groups | Pembrolizumab v Paclitaxel |

| | |
|---|---|
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.6901 [14] |
| Method | Miettinen and Nurminen method |
| Parameter estimate | Difference in Percentage |
| Point estimate | -1.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.5 |
| upper limit | 4 |

Notes:

[14] - Stratification factors for MN method included geographic region (Europe/Israel/North America/Australia vs. Asia vs. Rest of World), TTP on first-line therapy (<6 months vs. ≥6 months), and PD-L1 status (positive vs. negative) weighting by sample size

## Secondary: ORR According to RECIST 1.1 Based on Investigator Assessment in PD-L1 Positive Participants

| | |
|---|---|
| End point title | ORR According to RECIST 1.1 Based on Investigator Assessment in PD-L1 Positive Participants |

End point description:

ORR was defined as the percentage of the participants in the analysis population who had a confirmed CR (disappearance of all non-nodal target lesions and any pathological lymph nodes must have become normal) or PR (at least a 30% decrease in the SOD of target lesions, taking as reference the baseline SOD) according to RECIST 1.1 and based on investigator assessment. ORR was analyzed using the stratified Miettinen and Nurminen method, and reported with 95% CI for PD-L1 positive participants by treatment group. All randomized PD-L1 positive participants were analyzed. Participants were included in the treatment group to which they were randomized.

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

End point timeframe:

Up to 30 months (through database cut-off date of 26 Oct 2017)

| **End point values** | Pembrolizumab | Paclitaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 196 | 199 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 17.3 (12.3 to 23.4) | 15.6 (10.8 to 21.4) | | |

### Statistical analyses

| **Statistical analysis title** | ORR per RECIST 1.1 - PD-L1 positive participants |
|---|---|

Statistical analysis description:

Stratified MN method was used for comparison of the ORR between the treatment arms. A 95% CI for the difference in response rates between the pembrolizumab arm and paclitaxel arm was provided.

| | |
|---|---|
| Comparison groups | Pembrolizumab v Paclitaxel |

| | |
|---|---|
| Number of subjects included in analysis | 395 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.3322 [15] |
| Method | Miettinen and Nurminen method |
| Parameter estimate | Difference in Percentage |
| Point estimate | 1.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.8 |
| upper limit | 9.1 |

Notes:

[15] - Stratification factors for MN method included geographic region (Europe/Israel/North America/Australia vs. Asia vs. Rest of World) and TTP on first-line therapy (<6 months vs. ≥6 months), weighting by sample size.

## Secondary: ORR According to RECIST 1.1 Based on Investigator Assessment in All Participants

| | |
|---|---|
| End point title | ORR According to RECIST 1.1 Based on Investigator Assessment in All Participants |

End point description:

ORR was defined as the percentage of the participants in the analysis population who had a confirmed CR (disappearance of all non-nodal target lesions and any pathological lymph nodes must have become normal) or PR (at least a 30% decrease in the SOD of target lesions, taking as reference the baseline SOD) according to RECIST 1.1 and based on investigator assessment. ORR was analyzed using the stratified Miettinen and Nurminen method, and reported with 95% CI for all participants by treatment group. All randomized participants were analyzed. Participants were included in the treatment group to which they were randomized.

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

End point timeframe:

Up to 30 months (through database cut-off date of 26 Oct 2017)

| **End point values** | Pembrolizumab | Paclitaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 296 | 296 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 12.2 (8.7 to 16.4) | 15.2 (11.3 to 19.8) | | |

### Statistical analyses

| **Statistical analysis title** | ORR per RECIST 1.1 - all participants |
|---|---|

Statistical analysis description:

Stratified Miettinen and Nurminen's method was used for comparison of the ORR between the treatment arms. A 95% CI for the difference in response rates between the pembrolizumab arm and paclitaxel arm is provided.

| | |
|---|---|
| Comparison groups | Pembrolizumab v Paclitaxel |

| | |
|---|---|
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.85922 [16] |
| Method | Miettinen and Nurminen method |
| Parameter estimate | Difference in Percentage |
| Point estimate | -3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.5 |
| upper limit | 2.6 |

Notes:

[16] - Stratification factors included geographic region (Europe/Israel/North America/Australia vs. Asia vs. Rest of World), TTP on first-line therapy (<6 months vs. ≥6 months), and PD-L1 status (positive vs. negative) weighting by sample size.

## Secondary: Duration of Response (DOR) According to RECIST 1.1 Based on BICR in PD-L1 Positive Participants

| | |
|---|---|
| End point title | Duration of Response (DOR) According to RECIST 1.1 Based on BICR in PD-L1 Positive Participants |

End point description:

For PD-L1 positive participants who demonstrated CR (disappearance of all non-nodal target lesions and any pathological lymph nodes must have become normal) or PR (at least a 30% decrease in the SOD of target lesions, taking as reference the baseline SOD) according to RECIST 1.1 and based on BICR, DOR was defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first. DOR for participants who had not progressed or died at the time of analysis was censored at the date of their last tumor assessment. DOR was analyzed using the Kaplan-Meier method and median DOR (range) in months was reported for PD-L1 positive participants with response by treatment group. The subset of all randomized PD-L1 positive participants that showed a CR or PR according to RECIST 1.1 and based on BICR were analyzed. Participants were included in the treatment group to which they were randomized.

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

End point timeframe:

Up to 30 months (through database cut-off date of 26 Oct 2017)

| **End point values** | Pembrolizumab | Paclitaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 31 | 27 | | |
| Units: months | | | | |
| median (full range (min-max)) | 18.0 (1.4 to 26.0) | 5.2 (1.3 to 16.8) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: DOR According to RECIST 1.1 Based on BICR in All Participants

| | |
|---|---|
| End point title | DOR According to RECIST 1.1 Based on BICR in All Participants |

End point description:

For participants who demonstrated CR (disappearance of all non-nodal target lesions and any pathological lymph nodes must have become normal) or PR (at least a 30% decrease in the SOD of target lesions, taking as reference the baseline SOD) according to RECIST 1.1 and based on BICR, DOR was defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first. DOR for participants who had not progressed or died at the time of analysis was censored at the date of their last tumor assessment. DOR was analyzed using the Kaplan-Meier method and median DOR (range) in months was reported for all participants with response by treatment group. The subset of all randomized participants that showed a CR or PR according to RECIST 1.1 and based on BICR were analyzed. Participants were included in the treatment group to which they were randomized.

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

End point timeframe:

Up to 30 months (through database cut-off date of 26 Oct 2017)

| **End point values** | Pembrolizumab | Paclitaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 33 | 37 | | |
| Units: months | | | | |
| median (full range (min-max)) | 18.0 (1.4 to 26.0) | 5.5 (1.3 to 17.7) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: DOR According to RECIST 1.1 Based on Investigator Assessment in PD-L1 Positive Participants

| End point title | DOR According to RECIST 1.1 Based on Investigator Assessment in PD-L1 Positive Participants |
|---|---|

End point description:

For PD-L1 positive participants who demonstrated CR (disappearance of all non-nodal target lesions and any pathological lymph nodes must have become normal) or PR (at least a 30% decrease in the SOD of target lesions, taking as reference the baseline SOD) according to RECIST 1.1 and based on investigator assessment, DOR was defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first. DOR for participants who had not progressed or died at the time of analysis was censored at the date of their last tumor assessment. DOR was analyzed using the Kaplan-Meier method and median DOR (range) in months was reported for PD-L1 positive participants with response by treatment group. The subset of all randomized PD-L1 positive participants that showed a CR or PR according to RECIST 1.1 and based on investigator assessment were analyzed. Participants were included in the treatment group to which they were randomized.

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

End point timeframe:

Up to 30 months (through database cut-off date of 26 Oct 2017)

| End point values | Pembrolizumab | Paclitaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 34 | 31 | | |
| Units: months | | | | |
| median (full range (min-max)) | 15.7 (2.7 to 23.7) | 4.3 (1.8 to 19.1) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: DOR According to RECIST 1.1 Based on Investigator Assessment in All Participants

| End point title | DOR According to RECIST 1.1 Based on Investigator Assessment in All Participants |
|---|---|

End point description:

For participants who demonstrated CR (disappearance of all non-nodal target lesions and any pathological lymph nodes must have become normal) or PR (at least a 30% decrease in the SOD of target lesions, taking as reference the baseline SOD) according to RECIST 1.1 and based on investigator assessment, DOR was defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first. DOR for participants who had not progressed or died at the time of analysis was censored at the date of their last tumor assessment. DOR was analyzed using the Kaplan-Meier method and median DOR (range) in months was reported for all participants with response by treatment group. The subset of all randomized participants that showed a CR or PR according to RECIST 1.1 and based on investigator assessment were analyzed. Participants were included in the treatment group to which they were randomized.

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

End point timeframe:

Up to 30 months (through database cut-off date of 26 Oct 2017)

| End point values | Pembrolizumab | Paclitaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 36 | 45 | | |
| Units: months | | | | |
| median (full range (min-max)) | 15.7 (2.7 to 23.7) | 4.3 (1.3 to 19.1) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of PD-L1 Positive Participants Who Experienced an Adverse Event (AE)

| End point title | Percentage of PD-L1 Positive Participants Who Experienced an Adverse Event (AE) |
|---|---|

End point description:

An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE

could therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening of a pre-existing condition that was temporally associated with the use of the Sponsor’s product was also an AE. The percentage of participants with at least one AE was reported for PD-L1 positive participants by treatment group. All randomized PD-L1 positive participants who received at least 1 dose of study treatment were analyzed.

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

End point timeframe:

Up to 71 months (through database cut-off date of 10 Jun 2021)

| **End point values** | Pembrolizumab | Paclitaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 194 | 188 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 93.3 | 97.3 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of All Participants Who Experienced an AE

| End point title | Percentage of All Participants Who Experienced an AE |
|---|---|

End point description:

An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE could therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening of a pre-existing condition that was temporally associated with the use of the Sponsor’s product was also an AE. The percentage of participants with at least one AE was reported for all participants by treatment group. All randomized participants who received at least 1 dose of study treatment were analyzed.

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

End point timeframe:

Up to 71 months (through database cut-off date of 10 Jun 2021)

| **End point values** | Pembrolizumab | Paclitaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 294 | 276 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 93.9 | 97.1 | | |

### Statistical analyses

| Statistical analysis title | All participants |
|---|---|

Statistical analysis description:

Between-treatment differences (Pembrolizumab vs. Paclitaxel) in the percentage of participants with events and accompanying 95% confidence intervals were based on the Miettinen and Nurminen method. Negative values correspond to a greater percentage of events for Paclitaxel.

| | |
|---|---|
| Comparison groups | Pembrolizumab v Paclitaxel |
| Number of subjects included in analysis | 570 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Difference in Percentage |
| Point estimate | -3.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.9 |
| upper limit | 0.2 |

## Secondary: Percentage of PD-L1 Positive Participants that Discontinued Study Treatment Due to AE

| End point title | Percentage of PD-L1 Positive Participants that Discontinued Study Treatment Due to AE |
|---|---|

End point description:

An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE could therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening of a pre-existing condition that was temporally associated with the use of the Sponsor’s product was also an AE. The percentage of participants that discontinued study treatment due to an AE was reported for PD-L1 positive participants by treatment group. All randomized PD-L1 positive participants who received at least 1 dose of study treatment were analyzed.

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

End point timeframe:

Up to approximately 26.4 months

| End point values | Pembrolizumab | Paclitaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 194 | 188 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 4.1 | 8.0 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of All Participants that Discontinued Study Treatment Due to

## AE

| End point title | Percentage of All Participants that Discontinued Study Treatment Due to AE |
|---|---|

End point description:

An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE could therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening of a pre-existing condition that was temporally associated with the use of the Sponsor's product was also an AE. The percentage of participants that discontinued study treatment due to an AE was reported for all participants by treatment group. All randomized participants who received at least 1 dose of study treatment were analyzed.

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

End point timeframe:

Up to approximately 26.4 months

| **End point values** | Pembrolizumab | Paclitaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 294 | 276 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 4.8 | 9.1 | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 71 months (through database cut-off date of 10 Jun 2021)

Adverse event reporting additional description:

Deaths (all-causes) analysis population included all randomized participants (N=296, 296, 3). AE analysis population included all participants who received ≥1 dose of study treatment (N=294, 276, 3). MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" unrelated to study drug are excluded as AEs.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 24.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Pembrolizumab First Course |

Reporting group description:

Participants receive 200 mg IV pembrolizumab on Day 1 of each 21-day cycle, for up to 35 administrations (approximately 2 years).

| | |
|---|---|
| Reporting group title | Pembrolizumab Second Course |

Reporting group description:

Qualified participants who received pembrolizumab as a first course and stopped the first course of pembrolizumab due to complete response (CR) or completed the first course of pembrolizumab and had stable disease but progressed after discontinuation, initiated a second course of pembrolizumab at the investigator's discretion for up to 17 cycles (approximately 1 year additional).

| | |
|---|---|
| Reporting group title | Paclitaxel |

Reporting group description:

Participants receive paclitaxel 80 mg/m^2 IV, on Days 1, 8, and 15 of each 28-day cycle until disease progression or unacceptable toxicity.

| Serious adverse events | Pembrolizumab First Course | Pembrolizumab Second Course | Paclitaxel |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 108 / 296 (36.49%) | 1 / 3 (33.33%) | 68 / 296 (22.97%) |
| number of deaths (all causes) | 278 | 2 | 287 |
| number of deaths resulting from adverse events | 3 | 0 | 1 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Metastases to meninges | | | |
| subjects affected / exposed[1] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed[2] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed[3] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Shock haemorrhagic | | | |
| subjects affected / exposed[4] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 |
| Vascular compression | | | |
| subjects affected / exposed[5] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subclavian vein thrombosis | | | |
| subjects affected / exposed[6] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed[7] | 2 / 294 (0.68%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Complication associated with device | | | |
| subjects affected / exposed[8] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| 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[9] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 1 |

| | | | |
|---|---|---|---|
| Fatigue | | | |
| subjects affected / exposed[10] | 2 / 294 (0.68%) | 0 / 3 (0.00%) | 0 / 276 (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 |
| General physical health deterioration | | | |
| subjects affected / exposed[11] | 3 / 294 (1.02%) | 0 / 3 (0.00%) | 0 / 276 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza like illness | | | |
| subjects affected / exposed[12] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oedema peripheral | | | |
| subjects affected / exposed[13] | 2 / 294 (0.68%) | 0 / 3 (0.00%) | 0 / 276 (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 |
| Pyrexia | | | |
| subjects affected / exposed[14] | 5 / 294 (1.70%) | 0 / 3 (0.00%) | 4 / 276 (1.45%) |
| occurrences causally related to treatment / all | 2 / 7 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed[15] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Aspiration | | | |
| subjects affected / exposed[16] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 |
| Cough | | | |
| subjects affected / exposed[17] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 |

| | | | |
|---|---|---|---|
| Dyspnoea | | | |
| subjects affected / exposed[18] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 |
| Dyspnoea paroxysmal nocturnal | | | |
| subjects affected / exposed[19] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 |
| Interstitial lung disease | | | |
| subjects affected / exposed[20] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 |
| Pleural effusion | | | |
| subjects affected / exposed[21] | 3 / 294 (1.02%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed[22] | 3 / 294 (1.02%) | 0 / 3 (0.00%) | 2 / 276 (0.72%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed[23] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 |
| Pneumothorax | | | |
| subjects affected / exposed[24] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed[25] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 4 / 276 (1.45%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Respiratory failure | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed[26] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 | | | |
| Completed suicide | | | |
| subjects affected / exposed[27] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 |
| Confusional state | | | |
| subjects affected / exposed[28] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Panic disorder | | | |
| subjects affected / exposed[29] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Product issues | | | |
| Device dislocation | | | |
| subjects affected / exposed[30] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 |
| Device occlusion | | | |
| subjects affected / exposed[31] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed[32] | 2 / 294 (0.68%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed[33] | 2 / 294 (0.68%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Blood bilirubin increased | | | |
| subjects affected / exposed[34] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 |
| Weight decreased | | | |
| subjects affected / exposed[35] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed[36] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femoral neck fracture | | | |
| subjects affected / exposed[37] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hip fracture | | | |
| subjects affected / exposed[38] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Humerus fracture | | | |
| subjects affected / exposed[39] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 |
| Muscle strain | | | |
| subjects affected / exposed[40] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin wound | | | |
| subjects affected / exposed[41] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 |

| | | | |
|---|---|---|---|
| Toxicity to various agents | | | |
| subjects affected / exposed[42] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 stoma complication | | | |
| subjects affected / exposed[43] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wrist fracture | | | |
| subjects affected / exposed[44] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| 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 fibrillation | | | |
| subjects affected / exposed[45] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed[46] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 disorders | | | |
| Cerebral infarction | | | |
| subjects affected / exposed[47] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 |
| Cerebral ischaemia | | | |
| subjects affected / exposed[48] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 |
| Depressed level of consciousness | | | |
| subjects affected / exposed[49] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 |

| | | | |
|---|---|---|---|
| Epilepsy | | | |
| subjects affected / exposed[50] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intracranial mass | | | |
| subjects affected / exposed[51] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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[52] | 11 / 294 (3.74%) | 0 / 3 (0.00%) | 5 / 276 (1.81%) |
| occurrences causally related to treatment / all | 3 / 14 | 0 / 0 | 4 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Disseminated intravascular coagulation | | | |
| subjects affected / exposed[53] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Febrile neutropenia | | | |
| subjects affected / exposed[54] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Microcytic anaemia | | | |
| subjects affected / exposed[55] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed[56] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Splenic infarction | | | |
| subjects affected / exposed[57] | 0 / 294 (0.00%) | 1 / 3 (33.33%) | 0 / 276 (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 |

| | | | |
|---|---|---|---|
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed[58] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Retinal detachment | | | |
| subjects affected / exposed[59] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal adhesions | | | |
| subjects affected / exposed[60] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain | | | |
| subjects affected / exposed[61] | 8 / 294 (2.72%) | 1 / 3 (33.33%) | 4 / 276 (1.45%) |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 1 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain lower | | | |
| subjects affected / exposed[62] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed[63] | 4 / 294 (1.36%) | 0 / 3 (0.00%) | 0 / 276 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ascites | | | |
| subjects affected / exposed[64] | 4 / 294 (1.36%) | 0 / 3 (0.00%) | 2 / 276 (0.72%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed[65] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 3 / 276 (1.09%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 3 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Constipation | | | |
| subjects affected / exposed[66] | 5 / 294 (1.70%) | 0 / 3 (0.00%) | 4 / 276 (1.45%) |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Duodenal stenosis | | | |
| subjects affected / exposed[67] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 |
| Dyspepsia | | | |
| subjects affected / exposed[68] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| 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[69] | 2 / 294 (0.68%) | 0 / 3 (0.00%) | 2 / 276 (0.72%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric haemorrhage | | | |
| subjects affected / exposed[70] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 |
| Gastric hypomotility | | | |
| subjects affected / exposed[71] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric stenosis | | | |
| subjects affected / exposed[72] | 2 / 294 (0.68%) | 0 / 3 (0.00%) | 0 / 276 (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 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed[73] | 2 / 294 (0.68%) | 0 / 3 (0.00%) | 0 / 276 (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 |
| Gastrointestinal perforation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed[74] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 |
| Gastrosplenic fistula | | | |
| subjects affected / exposed[75] | 0 / 294 (0.00%) | 1 / 3 (33.33%) | 0 / 276 (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 |
| Haematemesis | | | |
| subjects affected / exposed[76] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 2 / 276 (0.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ileal perforation | | | |
| subjects affected / exposed[77] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Ileus | | | |
| subjects affected / exposed[78] | 4 / 294 (1.36%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Impaired gastric emptying | | | |
| subjects affected / exposed[79] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 |
| Intestinal obstruction | | | |
| subjects affected / exposed[80] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 4 / 276 (1.45%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 7 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Large intestinal obstruction | | | |
| subjects affected / exposed[81] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestine perforation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed[82] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Mechanical ileus | | | |
| subjects affected / exposed[83] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Melaena | | | |
| subjects affected / exposed[84] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed[85] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Obstruction gastric | | | |
| subjects affected / exposed[86] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 2 / 276 (0.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophageal obstruction | | | |
| subjects affected / exposed[87] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophageal stenosis | | | |
| subjects affected / exposed[88] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatic failure | | | |
| subjects affected / exposed[89] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed[90] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal haemorrhage | | | |
| subjects affected / exposed[91] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 |
| Small intestinal obstruction | | | |
| subjects affected / exposed[92] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subileus | | | |
| subjects affected / exposed[93] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed[94] | 3 / 294 (1.02%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed[95] | 6 / 294 (2.04%) | 0 / 3 (0.00%) | 2 / 276 (0.72%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Autoimmune hepatitis | | | |
| subjects affected / exposed[96] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bile duct stenosis | | | |
| subjects affected / exposed[97] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Biliary obstruction | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed[98] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 |
| Cholangitis | | | |
| subjects affected / exposed[99] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis acute | | | |
| subjects affected / exposed[100] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 |
| Cholelithiasis | | | |
| subjects affected / exposed[101] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis | | | |
| subjects affected / exposed[102] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed[103] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 |
| Jaundice cholestatic | | | |
| subjects affected / exposed[104] | 2 / 294 (0.68%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed[105] | 3 / 294 (1.02%) | 0 / 3 (0.00%) | 0 / 276 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic kidney disease | | | |

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|---|---|---|---|
| subjects affected / exposed[106] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysuria | | | |
| subjects affected / exposed[107] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematuria | | | |
| subjects affected / exposed[108] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydronephrosis | | | |
| subjects affected / exposed[109] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephrolithiasis | | | |
| subjects affected / exposed[110] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 |
| Renal failure | | | |
| subjects affected / exposed[111] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| Renal injury | | | |
| subjects affected / exposed[112] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 retention | | | |
| subjects affected / exposed[113] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 obstruction | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed[114] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Addison's disease | | | |
| subjects affected / exposed[115] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 |
| Hypophysitis | | | |
| subjects affected / exposed[116] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 |
| Hypopituitarism | | | |
| subjects affected / exposed[117] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 |
| Hypothyroidism | | | |
| subjects affected / exposed[118] | 2 / 294 (0.68%) | 0 / 3 (0.00%) | 0 / 276 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed[119] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 |
| Muscle disorder | | | |
| subjects affected / exposed[120] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Aspergillus infection | | | |
| subjects affected / exposed[121] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Bacteraemia | | | |
| subjects affected / exposed[122] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 |
| Bacterial sepsis | | | |
| subjects affected / exposed[123] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Biliary sepsis | | | |
| subjects affected / exposed[124] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 |
| Escherichia infection | | | |
| subjects affected / exposed[125] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enterobacter infection | | | |
| subjects affected / exposed[126] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed[127] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed[128] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 |
| Infection | | | |
| subjects affected / exposed[129] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infective exacerbation of chronic obstructive airways disease | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed[130] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 |
| Influenza | | | |
| subjects affected / exposed[131] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed[132] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 3 / 276 (1.09%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 2 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Medical device site infection | | | |
| subjects affected / exposed[133] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Otitis media | | | |
| subjects affected / exposed[134] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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[135] | 9 / 294 (3.06%) | 0 / 3 (0.00%) | 7 / 276 (2.54%) |
| occurrences causally related to treatment / all | 1 / 9 | 0 / 0 | 3 / 8 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Pneumonia bacterial | | | |
| subjects affected / exposed[136] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed[137] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 |
| Respiratory tract infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed[138] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed[139] | 2 / 294 (0.68%) | 0 / 3 (0.00%) | 3 / 276 (1.09%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Septic shock | | | |
| subjects affected / exposed[140] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| Urinary tract infection | | | |
| subjects affected / exposed[141] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed[142] | 2 / 294 (0.68%) | 0 / 3 (0.00%) | 0 / 276 (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 |
| Dehydration | | | |
| subjects affected / exposed[143] | 4 / 294 (1.36%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypercalcaemia | | | |
| subjects affected / exposed[144] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 |
| Hyperglycaemia | | | |
| subjects affected / exposed[145] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed[146] | 0 / 294 (0.00%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed[147] | 2 / 294 (0.68%) | 0 / 3 (0.00%) | 0 / 276 (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 |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed[148] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 0 / 276 (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 |

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: The analysis population includes all participants who received at least 1 dose of study treatment.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: The analysis population includes all participants who received at least 1 dose of study treatment.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: The analysis population includes all participants who received at least 1 dose of study treatment.

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
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[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
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Frequency threshold for reporting non-serious adverse events: 5 %

| **Non-serious adverse events** | Pembrolizumab First Course | Pembrolizumab Second Course | Paclitaxel |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 256 / 296 (86.49%) | 3 / 3 (100.00%) | 260 / 296 (87.84%) |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed[149] | 30 / 294 (10.20%) | 1 / 3 (33.33%) | 38 / 276 (13.77%) |
| occurrences (all) | 41 | 1 | 63 |
| Fatigue | | | |
| subjects affected / exposed[150] | 77 / 294 (26.19%) | 1 / 3 (33.33%) | 89 / 276 (32.25%) |
| occurrences (all) | 95 | 1 | 132 |
| Mucosal inflammation | | | |
| subjects affected / exposed[151] | 2 / 294 (0.68%) | 0 / 3 (0.00%) | 16 / 276 (5.80%) |
| occurrences (all) | 4 | 0 | 19 |
| Pyrexia | | | |
| subjects affected / exposed[152] | 32 / 294 (10.88%) | 2 / 3 (66.67%) | 30 / 276 (10.87%) |
| occurrences (all) | 40 | 2 | 38 |
| Oedema peripheral | | | |
| subjects affected / exposed[153] | 24 / 294 (8.16%) | 0 / 3 (0.00%) | 29 / 276 (10.51%) |
| occurrences (all) | 25 | 0 | 37 |
| Immune system disorders | | | |
| Seasonal allergy | | | |
| subjects affected / exposed[154] | 0 / 294 (0.00%) | 1 / 3 (33.33%) | 0 / 276 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|---|---|---|
| Cough | | | |
| subjects affected / exposed[155] | 18 / 294 (6.12%) | 0 / 3 (0.00%) | 28 / 276 (10.14%) |
| occurrences (all) | 18 | 0 | 34 |
| Dyspnoea | | | |
| subjects affected / exposed[156] | 25 / 294 (8.50%) | 0 / 3 (0.00%) | 19 / 276 (6.88%) |
| occurrences (all) | 27 | 0 | 22 |
| Dyspnoea exertional | | | |
| subjects affected / exposed[157] | 1 / 294 (0.34%) | 1 / 3 (33.33%) | 2 / 276 (0.72%) |
| occurrences (all) | 1 | 2 | 2 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed[158] | 16 / 294 (5.44%) | 0 / 3 (0.00%) | 24 / 276 (8.70%) |
| occurrences (all) | 16 | 0 | 26 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed[159] | 18 / 294 (6.12%) | 0 / 3 (0.00%) | 18 / 276 (6.52%) |
| occurrences (all) | 19 | 0 | 26 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed[160] | 24 / 294 (8.16%) | 0 / 3 (0.00%) | 16 / 276 (5.80%) |
| occurrences (all) | 26 | 0 | 22 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed[161] | 21 / 294 (7.14%) | 0 / 3 (0.00%) | 9 / 276 (3.26%) |
| occurrences (all) | 21 | 0 | 12 |
| Neutrophil count decreased | | | |
| subjects affected / exposed[162] | 2 / 294 (0.68%) | 0 / 3 (0.00%) | 36 / 276 (13.04%) |
| occurrences (all) | 5 | 0 | 70 |
| Weight decreased | | | |
| subjects affected / exposed[163] | 22 / 294 (7.48%) | 1 / 3 (33.33%) | 17 / 276 (6.16%) |
| occurrences (all) | 23 | 1 | 21 |
| White blood cell count decreased | | | |
| subjects affected / exposed[164] | 3 / 294 (1.02%) | 0 / 3 (0.00%) | 19 / 276 (6.88%) |
| occurrences (all) | 6 | 0 | 45 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed[165] | 14 / 294 (4.76%) | 0 / 3 (0.00%) | 15 / 276 (5.43%) |
| occurrences (all) | 15 | 0 | 18 |

| | | | |
|---|---|---|---|
| Headache | | | |
| subjects affected / exposed[166] | 10 / 294 (3.40%) | 0 / 3 (0.00%) | 15 / 276 (5.43%) |
| occurrences (all) | 12 | 0 | 20 |
| Neuropathy peripheral | | | |
| subjects affected / exposed[167] | 8 / 294 (2.72%) | 0 / 3 (0.00%) | 42 / 276 (15.22%) |
| occurrences (all) | 8 | 0 | 45 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed[168] | 5 / 294 (1.70%) | 0 / 3 (0.00%) | 37 / 276 (13.41%) |
| occurrences (all) | 5 | 0 | 43 |
| Sciatica | | | |
| subjects affected / exposed[169] | 0 / 294 (0.00%) | 1 / 3 (33.33%) | 0 / 276 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Syncope | | | |
| subjects affected / exposed[170] | 0 / 294 (0.00%) | 1 / 3 (33.33%) | 0 / 276 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed[171] | 44 / 294 (14.97%) | 1 / 3 (33.33%) | 68 / 276 (24.64%) |
| occurrences (all) | 56 | 1 | 86 |
| Neutropenia | | | |
| subjects affected / exposed[172] | 5 / 294 (1.70%) | 0 / 3 (0.00%) | 31 / 276 (11.23%) |
| occurrences (all) | 5 | 0 | 62 |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed[173] | 17 / 294 (5.78%) | 0 / 3 (0.00%) | 12 / 276 (4.35%) |
| occurrences (all) | 17 | 0 | 12 |
| Abdominal pain | | | |
| subjects affected / exposed[174] | 40 / 294 (13.61%) | 0 / 3 (0.00%) | 49 / 276 (17.75%) |
| occurrences (all) | 42 | 0 | 57 |
| Abdominal pain upper | | | |
| subjects affected / exposed[175] | 17 / 294 (5.78%) | 1 / 3 (33.33%) | 16 / 276 (5.80%) |
| occurrences (all) | 21 | 1 | 17 |
| Ascites | | | |
| subjects affected / exposed[176] | 19 / 294 (6.46%) | 0 / 3 (0.00%) | 12 / 276 (4.35%) |
| occurrences (all) | 19 | 0 | 14 |
| Constipation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed[177] | 56 / 294 (19.05%) | 0 / 3 (0.00%) | 53 / 276 (19.20%) |
| occurrences (all) | 62 | 0 | 71 |
| Diarrhoea | | | |
| subjects affected / exposed[178] | 40 / 294 (13.61%) | 1 / 3 (33.33%) | 72 / 276 (26.09%) |
| occurrences (all) | 42 | 2 | 104 |
| Dyspepsia | | | |
| subjects affected / exposed[179] | 18 / 294 (6.12%) | 0 / 3 (0.00%) | 11 / 276 (3.99%) |
| occurrences (all) | 18 | 0 | 13 |
| Dysphagia | | | |
| subjects affected / exposed[180] | 19 / 294 (6.46%) | 0 / 3 (0.00%) | 17 / 276 (6.16%) |
| occurrences (all) | 20 | 0 | 22 |
| Melaena | | | |
| subjects affected / exposed[181] | 6 / 294 (2.04%) | 1 / 3 (33.33%) | 1 / 276 (0.36%) |
| occurrences (all) | 6 | 1 | 1 |
| Nausea | | | |
| subjects affected / exposed[182] | 65 / 294 (22.11%) | 1 / 3 (33.33%) | 77 / 276 (27.90%) |
| occurrences (all) | 75 | 1 | 119 |
| Oesophageal pain | | | |
| subjects affected / exposed[183] | 2 / 294 (0.68%) | 1 / 3 (33.33%) | 1 / 276 (0.36%) |
| occurrences (all) | 2 | 1 | 1 |
| Stomatitis | | | |
| subjects affected / exposed[184] | 7 / 294 (2.38%) | 0 / 3 (0.00%) | 19 / 276 (6.88%) |
| occurrences (all) | 7 | 0 | 22 |
| Vomiting | | | |
| subjects affected / exposed[185] | 49 / 294 (16.67%) | 1 / 3 (33.33%) | 47 / 276 (17.03%) |
| occurrences (all) | 59 | 1 | 65 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed[186] | 1 / 294 (0.34%) | 0 / 3 (0.00%) | 116 / 276 (42.03%) |
| occurrences (all) | 1 | 0 | 120 |
| Dermatitis bullous | | | |
| subjects affected / exposed[187] | 0 / 294 (0.00%) | 1 / 3 (33.33%) | 0 / 276 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pruritus | | | |
| subjects affected / exposed[188] | 29 / 294 (9.86%) | 0 / 3 (0.00%) | 18 / 276 (6.52%) |
| occurrences (all) | 29 | 0 | 25 |

| | | | |
|---|---|---|---|
| Rash | | | |
| subjects affected / exposed[189] | 29 / 294 (9.86%) | 0 / 3 (0.00%) | 22 / 276 (7.97%) |
| occurrences (all) | 34 | 0 | 30 |
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed[190] | 22 / 294 (7.48%) | 0 / 3 (0.00%) | 1 / 276 (0.36%) |
| occurrences (all) | 25 | 0 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed[191] | 23 / 294 (7.82%) | 0 / 3 (0.00%) | 24 / 276 (8.70%) |
| occurrences (all) | 29 | 0 | 46 |
| Back pain | | | |
| subjects affected / exposed[192] | 33 / 294 (11.22%) | 0 / 3 (0.00%) | 23 / 276 (8.33%) |
| occurrences (all) | 37 | 0 | 29 |
| Groin pain | | | |
| subjects affected / exposed[193] | 1 / 294 (0.34%) | 1 / 3 (33.33%) | 1 / 276 (0.36%) |
| occurrences (all) | 2 | 1 | 1 |
| Myalgia | | | |
| subjects affected / exposed[194] | 9 / 294 (3.06%) | 0 / 3 (0.00%) | 25 / 276 (9.06%) |
| occurrences (all) | 10 | 0 | 31 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed[195] | 7 / 294 (2.38%) | 0 / 3 (0.00%) | 17 / 276 (6.16%) |
| occurrences (all) | 9 | 0 | 21 |
| Skin infection | | | |
| subjects affected / exposed[196] | 1 / 294 (0.34%) | 1 / 3 (33.33%) | 1 / 276 (0.36%) |
| occurrences (all) | 1 | 2 | 1 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed[197] | 76 / 294 (25.85%) | 0 / 3 (0.00%) | 79 / 276 (28.62%) |
| occurrences (all) | 83 | 0 | 99 |
| Hyperglycaemia | | | |
| subjects affected / exposed[198] | 7 / 294 (2.38%) | 1 / 3 (33.33%) | 2 / 276 (0.72%) |
| occurrences (all) | 8 | 1 | 21 |
| Hypoalbuminaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed[199] | 19 / 294 (6.46%) | 0 / 3 (0.00%) | 6 / 276 (2.17%) |
| occurrences (all) | 20 | 0 | 7 |
| Hypokalaemia | | | |
| subjects affected / exposed[200] | 15 / 294 (5.10%) | 0 / 3 (0.00%) | 10 / 276 (3.62%) |
| occurrences (all) | 17 | 0 | 11 |

Notes:

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## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 06 May 2015 | Amendment 02: Primary reason for amendment was to enable to better monitor disease response and progression based on evolving gastric cancer studies. Additionally, increasing the imaging interval after median progression may artificially lengthen the progression time in a substantial number of patients. Disease stratification factors (time to progression on first-line therapy and PD-L1 expression status) may help predict response in second-line gastric cancer treatment and consequently overall survival in gastric cancer patients. |
| 25 November 2015 | Amendment 05: Primary reason for amendment was due to the higher than anticipated prevalence rate for PD-L1+ patients, the interim futility analysis for PD-L1 patients is no longer necessary. |
| 24 August 2016 | Amendment 07: Primary reason for amendment was based on the recommendations from the external Data Monitoring Committee to no longer enroll PD-L1 negative participants as of 20-MAR-2016. |
| 06 September 2017 | Amendment 09: Primary reason for amendment was to update the timing to allow for adequate follow-up time before the final analysis in order to account for a potential delayed treatment effect on overall survival. |
| 15 November 2017 | Amendment 11: Primary reason for amendment was to clarify language in alignment with the labels – USPI and SmPC and the core data sheet and to add guidelines for the management of myocarditis to the table based upon health authority feedback; and to allow flexibility in the entire follow-up period beyond just the current survival follow-up portion to enable more frequent follow-ups as necessary. |
| 20 April 2020 | Amendment 13: Primary reason for amendment was to include an extension study. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported