

**Clinical trial results:****A Phase 3 Randomized, Double-Blind, Placebo-controlled Trial of Pembrolizumab (MK-3475/SCH900475) in Combination with Etoposide/Platinum (Cisplatin or Carboplatin) for the First-line Treatment of Subjects with Extensive Stage Small Cell Lung Cancer (KEYNOTE-604)****Summary**

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2016-004309-15    |
| Trial protocol           | DE GB ES PL FR HU |
| Global end of trial date | 21 September 2021 |

**Results information**

|                                |                   |
|--------------------------------|-------------------|
| Result version number          | v1 (current)      |
| This version publication date  | 22 September 2022 |
| First version publication date | 22 September 2022 |

**Trial information****Trial identification**

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 3475-604 |
|-----------------------|----------|

**Additional study identifiers**

|                                    |                                       |
|------------------------------------|---------------------------------------|
| ISRCTN number                      | -                                     |
| ClinicalTrials.gov id (NCT number) | NCT03066778                           |
| WHO universal trial number (UTN)   | -                                     |
| Other trial identifiers            | Merck: KEYNOTE-604, JAPIC-CTI: 173744 |

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                       | 21 September 2021 |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 02 December 2019  |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 21 September 2021 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

The purpose of this study is to assess the safety and efficacy of pembrolizumab plus standard of care (SOC) chemotherapy (etoposide/platinum [EP]) in participants with newly diagnosed extensive stage small cell lung cancer who have not previously received systemic therapy. The primary study hypotheses are that pembrolizumab+EP prolongs Progression-free Survival per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 by blinded independent central review and Overall Survival compared with placebo+EP. In this study, RECIST 1.1 has been modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. With protocol Amendment 07 (03-Oct-2018), the outcome measure of "Change from Baseline at Weeks 12 and 24 in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) Global Health Status/Quality of Life Scale" was replaced with a single time point analysis at Week 18.

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                          | 02 May 2017 |
| Long term follow-up planned                               | No          |
| Independent data monitoring committee (IDMC) involvement? | Yes         |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Australia: 14          |
| Country: Number of subjects enrolled | Canada: 32             |
| Country: Number of subjects enrolled | Chile: 14              |
| Country: Number of subjects enrolled | France: 25             |
| Country: Number of subjects enrolled | Germany: 12            |
| Country: Number of subjects enrolled | Hungary: 33            |
| Country: Number of subjects enrolled | Ireland: 4             |
| Country: Number of subjects enrolled | Israel: 29             |
| Country: Number of subjects enrolled | Japan: 35              |
| Country: Number of subjects enrolled | Korea, Republic of: 35 |
| Country: Number of subjects enrolled | Poland: 29             |
| Country: Number of subjects enrolled | Russian Federation: 25 |
| Country: Number of subjects enrolled | Spain: 39              |
| Country: Number of subjects enrolled | Switzerland: 14        |

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Taiwan: 14        |
| Country: Number of subjects enrolled | Turkey: 33        |
| Country: Number of subjects enrolled | United Kingdom: 9 |
| Country: Number of subjects enrolled | United States: 57 |
| Worldwide total number of subjects   | 453               |
| EEA total number of subjects         | 142               |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| 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)                      | 216 |
| From 65 to 84 years                       | 237 |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Participants in the pembrolizumab+EP arm were eligible to receive second course treatment with pembrolizumab if they met criteria for retreatment. Per protocol, response, progression, patient reported outcomes, or adverse events during second course did not count towards efficacy or safety outcome measures.

### Pre-assignment

Screening details:

One participant who was randomized to pembrolizumab+EP was inadvertently treated with placebo+EP. For efficacy analyses this participant will be included in the arm they were initially randomized into and for safety analyses the participant will be included by treatment received.

### Period 1

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

### Arms

|                              |                  |
|------------------------------|------------------|
| Are arms mutually exclusive? | Yes              |
| <b>Arm title</b>             | Pembrolizumab+EP |

Arm description:

During each 21-day cycle, participants received pembrolizumab 200 mg intravenously (IV) on Day 1 PLUS etoposide 100 mg/m<sup>2</sup> IV on Days 1, 2 and 3 PLUS investigator's choice of platinum therapy (carboplatin titrated to an area under the plasma drug concentration-time curve [AUC] 5 IV on Day 1 OR cisplatin 75 mg/m<sup>2</sup> IV on Day 1). Participants who stopped pembrolizumab as a result of obtaining a response of stable disease (SD), partial response (PR), complete response (CR) or those who stopped after receiving pembrolizumab for 24 months for reasons other than disease progression or intolerability, were eligible for up to an additional 1 year of treatment after progressive disease if they met the criteria for retreatment.

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

Dosage and administration details:

200 mg pembrolizumab administered by intravenous (IV) infusion on Day 1 of each 21-day cycle prior to chemotherapy

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

Dosage and administration details:

100 mg/m<sup>2</sup> etoposide administered by IV infusion on Days 1, 2, and 3 of each 21-day cycle

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

Dosage and administration details:

area under the plasma drug concentration-time curve (AUC) 5 carboplatin administered by IV infusion on Day 1 of each 21-day cycle

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

Dosage and administration details:

75 mg/m<sup>2</sup> cisplatin administered by IV infusion on Day 1 of each 21-day cycle

|                  |            |
|------------------|------------|
| <b>Arm title</b> | Placebo+EP |
|------------------|------------|

Arm description:

During each 21-day cycle, participants received placebo (normal saline solution) IV on Day 1 PLUS etoposide 100 mg/m<sup>2</sup> IV on Days 1, 2 and 3 PLUS investigator's choice of platinum therapy (carboplatin titrated to an AUC 5 IV on Day 1 OR cisplatin 75 mg/m<sup>2</sup> IV on Day 1).

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

Dosage and administration details:

saline placebo administered by IV infusion on Day 1 of each 21-day cycle prior to chemotherapy

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

Dosage and administration details:

100 mg/m<sup>2</sup> etoposide administered by IV infusion on Days 1, 2, and 3 of each 21-day cycle

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

Dosage and administration details:

area under the plasma drug concentration-time curve (AUC) 5 carboplatin administered by IV infusion on Day 1 of each 21-day cycle

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

Dosage and administration details:

75 mg/m<sup>2</sup> cisplatin administered by IV infusion on Day 1 of each 21-day cycle

| <b>Number of subjects in period 1</b>   | Pembrolizumab+EP | Placebo+EP       |
|---|------------------|------------------|
| Started                                 | 228              | 225              |
| Treated                                 | 223              | 223              |
| Received Second Course of Pembrolizumab | 1 <sup>[1]</sup> | 0 <sup>[2]</sup> |
| Completed                               | 28               | 13               |
| Not completed                           | 200              | 212              |
| Consent withdrawn by subject            | 5                | 7                |
| Death                                   | 195              | 205              |

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Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This milestone is for added to account for the participant that received a second course of pembrolizumab after the the initial study course was completed.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This milestone is for added to account for the participant that received a second course of pembrolizumab after the the initial study course was completed.

## Baseline characteristics

### Reporting groups

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Pembrolizumab+EP |
|-----------------------|------------------|

Reporting group description:

During each 21-day cycle, participants received pembrolizumab 200 mg intravenously (IV) on Day 1 PLUS etoposide 100 mg/m<sup>2</sup> IV on Days 1, 2 and 3 PLUS investigator's choice of platinum therapy (carboplatin titrated to an area under the plasma drug concentration-time curve [AUC] 5 IV on Day 1 OR cisplatin 75 mg/m<sup>2</sup> IV on Day 1). Participants who stopped pembrolizumab as a result of obtaining a response of stable disease (SD), partial response (PR), complete response (CR) or those who stopped after receiving pembrolizumab for 24 months for reasons other than disease progression or intolerability, were eligible for up to an additional 1 year of treatment after progressive disease if they met the criteria for retreatment.

|                       |            |
|-----------------------|------------|
| Reporting group title | Placebo+EP |
|-----------------------|------------|

Reporting group description:

During each 21-day cycle, participants received placebo (normal saline solution) IV on Day 1 PLUS etoposide 100 mg/m<sup>2</sup> IV on Days 1, 2 and 3 PLUS investigator's choice of platinum therapy (carboplatin titrated to an AUC 5 IV on Day 1 OR cisplatin 75 mg/m<sup>2</sup> IV on Day 1).

| Reporting group values                             | Pembrolizumab+EP | Placebo+EP | Total |
|--|------------------|------------|-------|
| Number of subjects                                 | 228              | 225        | 453   |
| Age categorical<br>Units: Subjects                 |                  |            |       |
| In utero   | 0                | 0          | 0     |
| Preterm newborn infants (gestational age < 37 wks) | 0                | 0          | 0     |
| Newborns (0-27 days)                               | 0                | 0          | 0     |
| Infants and toddlers (28 days-23 months)           | 0                | 0          | 0     |
| Children (2-11 years)                              | 0                | 0          | 0     |
| Adolescents (12-17 years)                          | 0                | 0          | 0     |
| Adults (18-64 years)                               | 115              | 101        | 216   |
| From 65-84 years                                   | 113              | 124        | 237   |
| 85 years and over                                  | 0                | 0          | 0     |
| Age Continuous<br>Units: Years                     |                  |            |       |
| arithmetic mean                                    | 64.2             | 65.2       | -     |
| standard deviation                                 | ± 8.4            | ± 8.2      | -     |
| Sex: Female, Male<br>Units: Participants           |                  |            |       |
| Female   | 76               | 83         | 159   |
| Male   | 152              | 142        | 294   |
| Race (NIH/OMB)<br>Units: Subjects                  |                  |            |       |
| American Indian or Alaska Native                   | 0                | 0          | 0     |
| Asian  | 52               | 34         | 86    |
| Native Hawaiian or Other Pacific Islander          | 0                | 0          | 0     |
| Black or African American                          | 1                | 0          | 1     |
| White  | 162              | 177        | 339   |
| More than one race                                 | 0                | 1          | 1     |
| Unknown or Not Reported                            | 13               | 13         | 26    |

|  |     |     |     |
|--|-----|-----|-----|
| Ethnicity (NIH/OMB)  |     |     |     |
| Units: Subjects  |     |     |     |
| Hispanic or Latino   | 6   | 13  | 19  |
| Not Hispanic or Latino   | 204 | 192 | 396 |
| Unknown or Not Reported  | 18  | 20  | 38  |
| Eastern Cooperative Oncology Group (ECOG) Performance Status   |     |     |     |
| An ECOG Performance Status of 0 (Fully active, able to carry on all pre-disease performance without restriction) or 1 (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature) was required for inclusion in the study and randomization was stratified by ECOG score. |     |     |     |
| Units: Subjects  |     |     |     |
| ECOG = 0   | 60  | 56  | 116 |
| ECOG = 1   | 168 | 169 | 337 |
| Lactate Dehydrogenase (LDH) Status at Baseline   |     |     |     |
| Randomization of participants in the study was stratified by LDH measurement at baseline ( $\leq$ or $>$ upper limit of normal).   |     |     |     |
| Units: Subjects  |     |     |     |
| LDH = $\leq$ Upper Limit of Normal   | 100 | 95  | 195 |
| LDH = $>$ Upper Limit of Normal  | 127 | 129 | 256 |
| LDH Result Missing   | 1   | 1   | 2   |
| Platinum Therapy Administered  |     |     |     |
| Randomization of participants was stratified by type of platinum therapy administered during the study.  |     |     |     |
| Units: Subjects  |     |     |     |
| Cisplatin  | 63  | 66  | 129 |
| Carboplatin  | 161 | 156 | 317 |
| Not Treated with Platinum Therapy  | 4   | 3   | 7   |



## End points

### End points reporting groups

|  |                  |
|--|------------------|
| Reporting group title  | Pembrolizumab+EP |
| Reporting group description:   |                  |
| During each 21-day cycle, participants received pembrolizumab 200 mg intravenously (IV) on Day 1 PLUS etoposide 100 mg/m <sup>2</sup> IV on Days 1, 2 and 3 PLUS investigator's choice of platinum therapy (carboplatin titrated to an area under the plasma drug concentration-time curve [AUC] 5 IV on Day 1 OR cisplatin 75 mg/m <sup>2</sup> IV on Day 1). Participants who stopped pembrolizumab as a result of obtaining a response of stable disease (SD), partial response (PR), complete response (CR) or those who stopped after receiving pembrolizumab for 24 months for reasons other than disease progression or intolerability, were eligible for up to an additional 1 year of treatment after progressive disease if they met the criteria for retreatment. |                  |
| Reporting group title  | Placebo+EP       |
| Reporting group description:   |                  |
| During each 21-day cycle, participants received placebo (normal saline solution) IV on Day 1 PLUS etoposide 100 mg/m <sup>2</sup> IV on Days 1, 2 and 3 PLUS investigator's choice of platinum therapy (carboplatin titrated to an AUC 5 IV on Day 1 OR cisplatin 75 mg/m <sup>2</sup> IV on Day 1).   |                  |

### Primary: Progression-free Survival (PFS) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR)

|  |  |
|--|--|
| End point title  | Progression-free Survival (PFS) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR) |
| End point description:   |  |
| PFS was defined as the time from randomization to the first documented progressive disease (PD) or death due to any cause, whichever occurred first. PD, as determined by RECIST 1.1, was defined as ≥20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of ≥5 mm. The appearance of one or more new lesions was also considered PD. For this study, RECIST 1.1 was modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. The analysis population consisted of all randomized participants who were included in the treatment group to which they were randomized. The PFS was calculated using the non-parametric Kaplan-Meier method (KM) for censored data and presented for the first course of study treatment per protocol. |  |
| End point type   | Primary  |
| End point timeframe:   |  |
| Up to approximately 30.5 months  |  |

| End point values                 | Pembrolizumab+EP | Placebo+EP       |  |  |
|----------------------------------|------------------|------------------|--|--|
| Subject group type               | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed      | 228              | 225              |  |  |
| Units: Months                    |                  |                  |  |  |
| median (confidence interval 95%) | 4.8 (4.3 to 5.4) | 4.3 (4.2 to 4.5) |  |  |

### Statistical analyses

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Hazard Ratio: Pembrolizumab+EP/Placebo+EP |
| Statistical analysis description:  |   |
| Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by platinum chemotherapy, ECOG, and LDH |   |
| Comparison groups  | Pembrolizumab+EP v Placebo+EP             |
| Number of subjects included in analysis  | 453                                       |
| Analysis specification   | Pre-specified                             |
| Analysis type  | superiority                               |
| P-value  | = 0.00069 <sup>[1]</sup>                  |
| Method   | Logrank                                   |
| Parameter estimate   | Hazard ratio (HR)                         |
| Point estimate   | 0.73                                      |
| Confidence interval  |   |
| level  | 95 %                                      |
| sides  | 2-sided                                   |
| lower limit  | 0.6                                       |
| upper limit  | 0.88                                      |

Notes:

[1] - One-sided p-value based on log-rank test stratified by platinum chemotherapy, ECOG, and LDH

### Primary: Overall Survival (OS)

|   |                       |
|---|-----------------------|
| End point title   | Overall Survival (OS) |
| 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 analysis were censored at the date of the last follow up. The analysis population consisted of all randomized participants who were included in the treatment group to which they were randomized. The OS was calculated using the non-parametric Kaplan-Meier method for censored data and presented for the first course of study treatment per protocol. |                       |
| End point type  | Primary               |
| End point timeframe:  |                       |
| Up to approximately 30.5 months   |                       |

| End point values                 | Pembrolizumab+EP   | Placebo+EP        |  |  |
|----------------------------------|--------------------|-------------------|--|--|
| Subject group type               | Reporting group    | Reporting group   |  |  |
| Number of subjects analysed      | 228                | 225               |  |  |
| Units: Months                    |                    |                   |  |  |
| median (confidence interval 95%) | 10.8 (9.2 to 12.9) | 9.7 (8.6 to 10.7) |  |  |

### Statistical analyses

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Hazard Ratio: Pembrolizumab+EP/Placebo+EP |
| Statistical analysis description:  |   |
| Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by platinum chemotherapy, ECOG, and LDH |   |
| Comparison groups  | Pembrolizumab+EP v Placebo+EP             |

|   |                          |
|---|--------------------------|
| Number of subjects included in analysis | 453                      |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | superiority              |
| P-value                                 | = 0.01643 <sup>[2]</sup> |
| Method                                  | Logrank                  |
| Parameter estimate                      | Hazard ratio (HR)        |
| Point estimate                          | 0.8                      |
| Confidence interval                     |                          |
| level                                   | 95 %                     |
| sides                                   | 2-sided                  |
| lower limit                             | 0.64                     |
| upper limit                             | 0.98                     |

Notes:

[2] - One-sided p-value based on log-rank test stratified by platinum chemotherapy, ECOG, and LDH

## Secondary: Objective Response Rate (ORR) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR)

|                 |  |
|-----------------|--|
| End point title | Objective Response Rate (ORR) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR) |
|-----------------|--|

End point description:

ORR was defined as the percentage of participants who achieve a best objective response of complete response (CR) or partial response (PR) per RECIST 1.1. CR was defined as the disappearance of all target lesions. PR was defined as  $\geq 30\%$  decrease in the sum of diameters of target lesions taking as a reference the baseline sum diameters. In this study, RECIST 1.1 was modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. The analysis population consisted of all randomized participants who were included in the treatment group to which they were randomized. The ORR was calculated using the Miettinen & Nurminen method stratified by type of platinum therapy (carboplatin or cisplatin), baseline ECOG performance status (0 or 1), and baseline LDH ( $\leq$  or  $>$  upper limit of normal) and presented for the first course of study treatment per protocol.

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

End point timeframe:

Up to approximately 30.5 months

| End point values                  | Pembrolizumab +EP   | Placebo+EP          |  |  |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type                | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed       | 228                 | 225                 |  |  |
| Units: Percentage of Participants |                     |                     |  |  |
| number (confidence interval 95%)  | 70.6 (64.2 to 76.4) | 61.8 (55.1 to 68.2) |  |  |

## Statistical analyses

|                            |                    |
|----------------------------|--------------------|
| Statistical analysis title | Percent Difference |
|----------------------------|--------------------|

Statistical analysis description:

Based on Miettinen & Nurminen method stratified by platinum chemotherapy, ECOG, and LDH. Cisplatin, ECOG 0, LDH  $\leq$ ULN and Cisplatin, ECOG 0, LDH  $>$ ULN were combined into one stratum because of small sample size

|   |                               |
|---|-------------------------------|
| Comparison groups                       | Pembrolizumab+EP v Placebo+EP |
| Number of subjects included in analysis | 453                           |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | superiority                   |
| P-value                                 | = 0.0227 <sup>[3]</sup>       |
| Method                                  | Miettinen & Nurminen          |
| Parameter estimate                      | Percent Difference            |
| Point estimate                          | 8.9                           |
| Confidence interval                     |                               |
| level                                   | 95 %                          |
| sides                                   | 2-sided                       |
| lower limit                             | 0.2                           |
| upper limit                             | 17.4                          |

Notes:

[3] - One-sided p-value for testing. H0: difference in percent = 0 versus H1: difference in percent >0

### Secondary: Duration of Response (DOR) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR)

|                 |   |
|-----------------|---|
| End point title | Duration of Response (DOR) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR) |
|-----------------|---|

End point description:

DOR was defined as the time from first documented evidence of a CR or PR per RECIST 1.1 until first instance of PD per RECIST 1.1 or death of any cause. CR=disappearance of all target lesions. PR= $\geq 30\%$  decrease in the sum of diameters (SOD) of target lesions taking the baseline SOD as reference. PD= $\geq 20\%$  increase in SOD. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of  $\geq 5$  mm. The appearance of  $\geq 1$  new lesions was also considered PD. RECIST 1.1 was modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. The analysis population=all randomized participants who were included in the treatment group to which they were randomized and experienced a CR or PR. The DOR was calculated using the KM method for censored data and is presented for the first course of study treatment per protocol. 9999=median DOR and upper and lower limits not reached due to no progressive disease by time of last disease assessment.

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

End point timeframe:

Up to approximately 30.5 months

| End point values              | Pembrolizumab+EP    | Placebo+EP          |  |  |
|-------------------------------|---------------------|---------------------|--|--|
| Subject group type            | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed   | 161                 | 139                 |  |  |
| Units: Months                 |                     |                     |  |  |
| median (full range (min-max)) | 9999 (9999 to 9999) | 9999 (9999 to 9999) |  |  |

### Statistical analyses

No statistical analyses for this end point

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

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

### End point description:

An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which did not necessarily have to have had a causal relationship with this treatment. An adverse event could be any unfavourable and unintended sign (i.e. abnormal laboratory finding), 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 (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that was temporally associated with the use of the Sponsor's product, was also an adverse event. The analysis population consisted of all participants who received  $\geq 1$  dose of study treatment. The number of participants who experienced an AE was reported for each arm according to the treatment received and is presented for the first course of study treatment per protocol.

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

### End point timeframe:

Up to approximately 30.5 months

| End point values            | Pembrolizumab +EP | Placebo+EP      |  |  |
|-----------------------------|-------------------|-----------------|--|--|
| Subject group type          | Reporting group   | Reporting group |  |  |
| Number of subjects analysed | 223               | 223             |  |  |
| Units: Participants         | 223               | 222             |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants Discontinuing Study Treatment Due to an Adverse Event (AE)

|                 |   |
|-----------------|---|
| End point title | Number of Participants Discontinuing Study Treatment Due to 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 did not necessarily have to have had a causal relationship with this treatment. An adverse event could be any unfavourable and unintended sign (i.e. abnormal laboratory finding), 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 (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that was temporally associated with the use of the Sponsor's product, was also an adverse event. The analysis population consisted of all participants who received  $\geq 1$  dose of study treatment. The number of participants who discontinued due to an AE was reported for each arm according to treatment received and is presented for the first course of study treatment per protocol.

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

### End point timeframe:

Up to approximately 26 months

| End point values            | Pembrolizumab +EP | Placebo+EP      |  |  |
|-----------------------------|-------------------|-----------------|--|--|
| Subject group type          | Reporting group   | Reporting group |  |  |
| Number of subjects analysed | 223               | 223             |  |  |
| Units: Participants         | 33                | 14              |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants Experiencing Any Grade 3 to 5 Adverse Events (AE) as Assessed by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 4.03 (CTCAE 4.03)

|                 |  |
|-----------------|--|
| End point title | Number of Participants Experiencing Any Grade 3 to 5 Adverse Events (AE) as Assessed by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 4.03 (CTCAE 4.03) |
|-----------------|--|

#### End point description:

The CTCAE uses Grades 1 through 5 correlating to AE severity criteria. Grade 1=mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. Grade 2=moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Grade 3=severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. Grade 4=life-threatening consequences; urgent intervention indicated. Grade 5=death related to AE. The analysis population consisted of all participants who received  $\geq 1$  dose of study treatment. The number of participants who experienced any Grade 3 to 5 AE was reported for each arm according to the treatment received and is presented for the first course of study treatment per protocol.

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

#### End point timeframe:

Up to approximately 30.5 months

| End point values            | Pembrolizumab +EP | Placebo+EP      |  |  |
|-----------------------------|-------------------|-----------------|--|--|
| Subject group type          | Reporting group   | Reporting group |  |  |
| Number of subjects analysed | 223               | 223             |  |  |
| Units: Participants         | 175               | 172             |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline at Week 18 in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) Global Health Status/Quality of Life Scale

|                 |  |
|-----------------|--|
| End point title | Change from Baseline at Week 18 in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) Global Health Status/Quality of Life Scale |
|-----------------|--|

**End point description:**

EORTC QLQ-C30 is a questionnaire that rates the overall quality of life in cancer participants. The first 28 questions use a 4-point scale (1=not at all-4=very much) for evaluating function (physical, role, social, cognitive, emotional), symptoms (diarrhea, fatigue, dyspnea, appetite loss, insomnia, nausea/vomiting, constipation, pain) and financial difficulties. The last 2 questions use a 7-point scale (1=very poor-7=excellent) to evaluate overall health and quality of life. Scores are transformed to a range of 0-100 using a standard algorithm. Change from baseline scores were calculated using a constrained longitudinal data analysis model. Negative change from baseline values indicated deterioration in health status or functioning; positive change indicated improvement. The analysis population=all participants who received  $\geq 1$  dose of study medication and had non-missing assessments at baseline and Week 18. Data are presented for the first course of study treatment per protocol.

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

**End point timeframe:**

Baseline (prior to first dose of study treatment in Cycle 1 [cycle length = 21 days]) and Week 18

| <b>End point values</b>                      | Pembrolizumab+EP     | Placebo+EP          |  |  |
|--|----------------------|---------------------|--|--|
| Subject group type                           | Reporting group      | Reporting group     |  |  |
| Number of subjects analysed                  | 221                  | 218                 |  |  |
| Units: Score on a Scale                      |                      |                     |  |  |
| least squares mean (confidence interval 95%) | 8.66 (5.26 to 12.06) | 4.23 (0.93 to 7.52) |  |  |

**Statistical analyses**

| <b>Statistical analysis title</b>       | Difference in Least Square Means |
|---|----------------------------------|
| Comparison groups                       | Pembrolizumab+EP v Placebo+EP    |
| Number of subjects included in analysis | 439                              |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           | other                            |
| P-value                                 | = 0.04                           |
| Method                                  | Logrank                          |
| Parameter estimate                      | Difference in Least Square Means |
| Point estimate                          | 4.43                             |
| Confidence interval                     |                                  |
| level                                   | 95 %                             |
| sides                                   | 2-sided                          |
| lower limit                             | 0.21                             |
| upper limit                             | 8.66                             |

**Secondary: Change from Baseline at Week 12 in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) Global Health Status/Quality of Life Scale**

|                 |  |
|-----------------|--|
| End point title | Change from Baseline at Week 12 in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) Global Health Status/Quality of Life Scale |
|-----------------|--|

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**End point description:**

EORTC QLQ-C30 is a questionnaire that rates the overall quality of life in cancer participants. The first 28 questions use a 4-point scale (1=not at all-4=very much) for evaluating function (physical, role, social, cognitive, emotional), symptoms (diarrhea, fatigue, dyspnea, appetite loss, insomnia, nausea/vomiting, constipation, pain) and financial difficulties. The last 2 questions use a 7-point scale (1=very poor-7=excellent) to evaluate overall health and quality of life. Scores are transformed to a range of 0-100 using a standard algorithm. Negative change from baseline values indicated deterioration in health status or functioning; positive change indicated improvement. The analysis population included all participants who received  $\geq 1$  dose of treatment and had non-missing assessments at baseline and Week 12. Per protocol data were to be presented for the first course of study treatment.

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

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**End point timeframe:**

Baseline (prior to first dose of study treatment in Cycle 1 [cycle length = 21 days]) and Week 12

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| End point values                             | Pembrolizumab +EP | Placebo+EP       |  |  |
|--|-------------------|------------------|--|--|
| Subject group type                           | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed                  | 0 <sup>[4]</sup>  | 0 <sup>[5]</sup> |  |  |
| Units: Score on a Scale                      |                   |                  |  |  |
| least squares mean (confidence interval 95%) | ( to )            | ( to )           |  |  |

**Notes:**

[4] - This outcome measure was replaced with a single time-point analysis at Week 18 with Amendment 7.

[5] - This outcome measure was replaced with a single time-point analysis at Week 18 with Amendment 7.

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**Statistical analyses**

No statistical analyses for this end point

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**Secondary: Change from Baseline at Week 24 in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) Global Health Status/Quality of Life Scale**

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|                 |  |
|-----------------|--|
| End point title | Change from Baseline at Week 24 in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) Global Health Status/Quality of Life Scale |
|-----------------|--|

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**End point description:**

EORTC QLQ-C30 is a questionnaire that rates the overall quality of life in cancer participants. The first 28 questions use a 4-point scale (1=not at all-4=very much) for evaluating function (physical, role, social, cognitive, emotional), symptoms (diarrhea, fatigue, dyspnea, appetite loss, insomnia, nausea/vomiting, constipation, pain) and financial difficulties. The last 2 questions use a 7-point scale (1=very poor-7=excellent) to evaluate overall health and quality of life. Scores are transformed to a range of 0-100 using a standard algorithm. Negative change from baseline values indicated deterioration in health status or functioning; positive change indicated improvement. The analysis population included all participants who received  $\geq 1$  dose of treatment and had non-missing assessments at baseline and Week 24. Per protocol, data were to be presented for the first course of study treatment.

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

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**End point timeframe:**

Baseline (prior to first dose of study treatment in Cycle 1 [cycle length = 21 days]) and Week 24

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| End point values                             | Pembrolizumab +EP | Placebo+EP       |  |  |
|--|-------------------|------------------|--|--|
| Subject group type                           | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed                  | 0 <sup>[6]</sup>  | 0 <sup>[7]</sup> |  |  |
| Units: Score on a Scale                      |                   |                  |  |  |
| least squares mean (confidence interval 95%) | ( to )            | ( to )           |  |  |

Notes:

[6] - This outcome measure was replaced with a single time-point analysis at Week 18 with Amendment 7.

[7] - This outcome measure was replaced with a single time-point analysis at Week 18 with Amendment 7.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to True Deterioration (TTD) in the Composite Endpoint of Cough, Chest Pain, and Dyspnea Using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and Lung Cancer Module 13 (QLQ-LC13)

|                 |  |
|-----------------|--|
| End point title | Time to True Deterioration (TTD) in the Composite Endpoint of Cough, Chest Pain, and Dyspnea Using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and Lung Cancer Module 13 (QLQ-LC13) |
|-----------------|--|

End point description:

TTD in patient-reported lung cancer symptoms of cough (QLQ-LC-13 Item 1), chest pain (QLQ-LC-13 Item 10), and dyspnea (QLQ-C30 Item 8) was a composite endpoint defined as: time to first onset of  $\geq 10$  point deterioration from baseline in an item confirmed by a second adjacent  $\geq 10$  point deterioration. The QLQ-LC13 consists of 13 measures of lung cancer symptoms and side effects from chemotherapy/radiation scored on a 4-point scale (1=none, 2=a little, 3=quite a bit, 4=very much). Scores were transformed to a range of 0-100 using a standard algorithm. Higher scores represented increasing symptom severity. The analysis population=all participants who received  $\geq 1$  dose of study medication and had non-missing assessments. TTD was calculated using the product-limit KM method for censored data and is presented for the first course of study treatment per protocol. 9999=Median TTD, lower or upper limit not reached (no protocol-specified deterioration criteria reached by time of last assessment).

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

End point timeframe:

Day 1 of Cycles 1-9, Day 1 of every other cycle for Cycles 10-17 and 30 days after last dose of study treatment (Up to approximately 27 months)]

| End point values                 | Pembrolizumab +EP   | Placebo+EP        |  |  |
|----------------------------------|---------------------|-------------------|--|--|
| Subject group type               | Reporting group     | Reporting group   |  |  |
| Number of subjects analysed      | 221                 | 218               |  |  |
| Units: Months                    |                     |                   |  |  |
| median (confidence interval 95%) | 9999 (9999 to 9999) | 8.7 (5.9 to 9999) |  |  |

## Statistical analyses

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Hazard Ratio: Pembrolizumab+EP/Placebo+EP |
| Statistical analysis description:  |   |
| Based on Cox regression model with treatment as a covariate stratified by platinum chemotherapy ECOG, and LDH. Cisplatin, ECOG 0, LDH ≤ULN and Cisplatin, ECOG 0, LDH >ULN were combined into one stratum because of small sample size |   |
| Comparison groups  | Pembrolizumab+EP v Placebo+EP             |
| Number of subjects included in analysis  | 439                                       |
| Analysis specification   | Pre-specified                             |
| Analysis type  | other                                     |
| P-value  | = 0.208 <sup>[8]</sup>                    |
| Method   | Logrank                                   |
| Parameter estimate   | Hazard ratio (HR)                         |
| Point estimate   | 0.8                                       |
| Confidence interval  |   |
| level  | 95 %                                      |
| sides  | 2-sided                                   |
| lower limit  | 0.56                                      |
| upper limit  | 1.14                                      |

Notes:

[8] - Two-sided p-value based on stratified log-rank test

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

First Course: Up to 49.5 months; Second Course: Up to 37.9 months. First and second course dosing occurred concurrently

Adverse event reporting additional description:

All-cause mortality (ACM)=all randomized participants; AE=participants treated  $\geq 1$  dose. Per protocol, MedDRA terms neoplasm progression (NP), malignant NP, disease progression unrelated to treatment are excluded. ACM was adjusted for participant randomized to pembrolizumab+EP and treated with placebo+EP. AEs presented by actual treatment received.

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

### Dictionary used

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

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

### Reporting groups

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Pembrolizumab+EP |
|-----------------------|------------------|

Reporting group description:

During each 21-day cycle, participants received pembrolizumab 200 mg intravenously (IV) on Day 1 PLUS etoposide 100 mg/m<sup>2</sup> IV on Days 1, 2 and 3 PLUS investigator's choice of platinum therapy (carboplatin titrated to an area under the plasma drug concentration-time curve [AUC] 5 IV on Day 1 OR cisplatin 75 mg/m<sup>2</sup> IV on Day 1). Participants who stopped pembrolizumab as a result of obtaining a response of stable disease (SD), partial response (PR), complete response (CR) or those who stopped after receiving pembrolizumab for 24 months for reasons other than disease progression or intolerability, were eligible for up to an additional 1 year of treatment after progressive disease if they met the criteria for retreatment.

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

Reporting group description:

Participants who met the criteria for retreatment received pembrolizumab 200 mg by IV infusion on Day 1 of each 21-day cycle for up to 1 year of treatment.

|                       |            |
|-----------------------|------------|
| Reporting group title | Placebo+EP |
|-----------------------|------------|

Reporting group description:

During each 21-day cycle, participants received placebo (normal saline solution) IV on Day 1 PLUS etoposide 100 mg/m<sup>2</sup> IV on Days 1, 2 and 3 PLUS investigator's choice of platinum therapy (carboplatin titrated to an AUC 5 IV on Day 1 OR cisplatin 75 mg/m<sup>2</sup> IV on Day 1).

| Serious adverse events  | Pembrolizumab+EP   | Pembrolizumab Second Course | Placebo+EP        |
|---|--------------------|-----------------------------|-------------------|
| Total subjects affected by serious adverse events                   |                    |                             |                   |
| subjects affected / exposed   | 111 / 223 (49.78%) | 1 / 1 (100.00%)             | 89 / 223 (39.91%) |
| number of deaths (all causes)                                       | 196                | 1                           | 212               |
| number of deaths resulting from adverse events                      | 6                  | 0                           | 6                 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                    |                             |                   |
| Cancer pain   |                    |                             |                   |
| subjects affected / exposed   | 0 / 223 (0.00%)    | 0 / 1 (0.00%)               | 2 / 223 (0.90%)   |
| occurrences causally related to treatment / all                     | 0 / 0              | 0 / 0                       | 0 / 2             |
| deaths causally related to treatment / all                          | 0 / 0              | 0 / 0                       | 0 / 0             |
| Paraneoplastic syndrome   |                    |                             |                   |

|   |                 |               |                 |
|---|-----------------|---------------|-----------------|
| subjects affected / exposed                     | 0 / 223 (0.00%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Colon cancer                                    |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Vascular disorders                              |                 |               |                 |
| Aortic aneurysm                                 |                 |               |                 |
| subjects affected / exposed                     | 2 / 223 (0.90%) | 0 / 1 (0.00%) | 0 / 223 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0         | 0 / 0           |
| Deep vein thrombosis                            |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Embolism  |                 |               |                 |
| subjects affected / exposed                     | 0 / 223 (0.00%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Hypertensive crisis                             |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Hypotension                                     |                 |               |                 |
| subjects affected / exposed                     | 2 / 223 (0.90%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0         | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Peripheral artery occlusion                     |                 |               |                 |
| subjects affected / exposed                     | 0 / 223 (0.00%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Peripheral embolism                             |                 |               |                 |

|  |                 |               |                 |
|--|-----------------|---------------|-----------------|
| subjects affected / exposed                          | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Superior vena cava syndrome                          |                 |               |                 |
| subjects affected / exposed                          | 2 / 223 (0.90%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all      | 1 / 2           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0         | 0 / 0           |
| Vena cava thrombosis                                 |                 |               |                 |
| subjects affected / exposed                          | 0 / 223 (0.00%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0         | 0 / 0           |
| General disorders and administration site conditions |                 |               |                 |
| Asthenia   |                 |               |                 |
| subjects affected / exposed                          | 3 / 223 (1.35%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all      | 1 / 3           | 0 / 0         | 1 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0         | 0 / 0           |
| Chest pain   |                 |               |                 |
| subjects affected / exposed                          | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Death  |                 |               |                 |
| subjects affected / exposed                          | 4 / 223 (1.79%) | 0 / 1 (0.00%) | 3 / 223 (1.35%) |
| occurrences causally related to treatment / all      | 0 / 4           | 0 / 0         | 3 / 3           |
| deaths causally related to treatment / all           | 0 / 4           | 0 / 0         | 3 / 3           |
| Fatigue  |                 |               |                 |
| subjects affected / exposed                          | 0 / 223 (0.00%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0         | 0 / 0           |
| Oedema peripheral                                    |                 |               |                 |
| subjects affected / exposed                          | 0 / 223 (0.00%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0         | 0 / 0           |
| Pain   |                 |               |                 |

|   |                 |               |                 |
|---|-----------------|---------------|-----------------|
| subjects affected / exposed                     | 0 / 223 (0.00%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Pyrexia   |                 |               |                 |
| subjects affected / exposed                     | 4 / 223 (1.79%) | 0 / 1 (0.00%) | 2 / 223 (0.90%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 0         | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Reproductive system and breast disorders        |                 |               |                 |
| Benign prostatic hyperplasia                    |                 |               |                 |
| subjects affected / exposed                     | 0 / 223 (0.00%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Prostatitis                                     |                 |               |                 |
| subjects affected / exposed                     | 0 / 223 (0.00%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders |                 |               |                 |
| Bronchospasm                                    |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Chronic obstructive pulmonary disease           |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Dyspnoea  |                 |               |                 |
| subjects affected / exposed                     | 3 / 223 (1.35%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Epistaxis                                       |                 |               |                 |

|   |                 |               |                 |
|---|-----------------|---------------|-----------------|
| subjects affected / exposed                     | 0 / 223 (0.00%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Haemoptysis                                     |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 2 / 223 (0.90%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0         | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 1           |
| Hypoxia   |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Laryngeal haemorrhage                           |                 |               |                 |
| subjects affected / exposed                     | 0 / 223 (0.00%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Oropharyngeal pain                              |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Pleural effusion                                |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 3 / 223 (1.35%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0         | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Pneumonitis                                     |                 |               |                 |
| subjects affected / exposed                     | 5 / 223 (2.24%) | 0 / 1 (0.00%) | 3 / 223 (1.35%) |
| occurrences causally related to treatment / all | 5 / 5           | 0 / 0         | 3 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 1 / 1           |
| Pneumothorax                                    |                 |               |                 |
| subjects affected / exposed                     | 2 / 223 (0.90%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Pulmonary embolism                              |                 |               |                 |

|   |                 |               |                 |
|---|-----------------|---------------|-----------------|
| subjects affected / exposed                     | 5 / 223 (2.24%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 1 / 5           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Respiratory failure                             |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 2 / 223 (0.90%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0         | 0 / 2           |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0         | 0 / 2           |
| Psychiatric disorders                           |                 |               |                 |
| Confusional state                               |                 |               |                 |
| subjects affected / exposed                     | 0 / 223 (0.00%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Investigations                                  |                 |               |                 |
| Alanine aminotransferase increased              |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Aspartate aminotransferase increased            |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0         | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Blood creatinine increased                      |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0         | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Injury, poisoning and procedural complications  |                 |               |                 |
| Fall  |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Infusion related reaction                       |                 |               |                 |



|   |                 |               |                 |
|---|-----------------|---------------|-----------------|
| subjects affected / exposed                     | 2 / 223 (0.90%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0         | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Femur fracture                                  |                 |               |                 |
| subjects affected / exposed                     | 0 / 223 (0.00%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Joint injury                                    |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Skin laceration                                 |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Spinal fracture                                 |                 |               |                 |
| subjects affected / exposed                     | 0 / 223 (0.00%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| 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                               |                 |               |                 |
| Acute coronary syndrome                         |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Atrial fibrillation                             |                 |               |                 |
| subjects affected / exposed                     | 4 / 223 (1.79%) | 0 / 1 (0.00%) | 3 / 223 (1.35%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 0         | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Cardiac arrest                                  |                 |               |                 |
| subjects affected / exposed                     | 0 / 223 (0.00%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 1           |
| Cardiac failure                                 |                 |               |                 |

|   |                 |               |                 |
|---|-----------------|---------------|-----------------|
| subjects affected / exposed                     | 0 / 223 (0.00%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 1 / 1           |
| Cardiopulmonary failure                         |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Myocardial infarction                           |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Myocarditis                                     |                 |               |                 |
| subjects affected / exposed                     | 0 / 223 (0.00%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Pericardial effusion                            |                 |               |                 |
| subjects affected / exposed                     | 0 / 223 (0.00%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Nervous system disorders                        |                 |               |                 |
| Aphasia   |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Cerebrovascular accident                        |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Cognitive disorder                              |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Dizziness                                       |                 |               |                 |

|   |                 |               |                 |
|---|-----------------|---------------|-----------------|
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Hemiparesis                                     |                 |               |                 |
| subjects affected / exposed                     | 2 / 223 (0.90%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Limbic encephalitis                             |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Loss of consciousness                           |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Peripheral motor neuropathy                     |                 |               |                 |
| subjects affected / exposed                     | 0 / 223 (0.00%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Presyncope                                      |                 |               |                 |
| subjects affected / exposed                     | 0 / 223 (0.00%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Toxic encephalopathy                            |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Transient ischaemic attack                      |                 |               |                 |
| subjects affected / exposed                     | 2 / 223 (0.90%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Tremor  |                 |               |                 |

|   |                  |                 |                  |
|---|------------------|-----------------|------------------|
| subjects affected / exposed                     | 1 / 223 (0.45%)  | 0 / 1 (0.00%)   | 0 / 223 (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            |
| Parkinsonism                                    |                  |                 |                  |
| subjects affected / exposed                     | 0 / 223 (0.00%)  | 1 / 1 (100.00%) | 0 / 223 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1           | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0            |
| Syncope   |                  |                 |                  |
| subjects affected / exposed                     | 1 / 223 (0.45%)  | 0 / 1 (0.00%)   | 0 / 223 (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                     | 7 / 223 (3.14%)  | 0 / 1 (0.00%)   | 10 / 223 (4.48%) |
| occurrences causally related to treatment / all | 6 / 7            | 0 / 0           | 8 / 10           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0            |
| Febrile neutropenia                             |                  |                 |                  |
| subjects affected / exposed                     | 15 / 223 (6.73%) | 0 / 1 (0.00%)   | 14 / 223 (6.28%) |
| occurrences causally related to treatment / all | 15 / 15          | 0 / 0           | 13 / 14          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0            |
| Leukopenia                                      |                  |                 |                  |
| subjects affected / exposed                     | 1 / 223 (0.45%)  | 0 / 1 (0.00%)   | 1 / 223 (0.45%)  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           | 1 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0            |
| Neutropenia                                     |                  |                 |                  |
| subjects affected / exposed                     | 11 / 223 (4.93%) | 0 / 1 (0.00%)   | 6 / 223 (2.69%)  |
| occurrences causally related to treatment / all | 10 / 11          | 0 / 0           | 6 / 6            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0            |
| Thrombocytopenia                                |                  |                 |                  |
| subjects affected / exposed                     | 3 / 223 (1.35%)  | 0 / 1 (0.00%)   | 5 / 223 (2.24%)  |
| occurrences causally related to treatment / all | 3 / 3            | 0 / 0           | 6 / 6            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0            |
| Ear and labyrinth disorders                     |                  |                 |                  |

|   |                 |               |                 |
|---|-----------------|---------------|-----------------|
| Vertigo   |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Eye disorders                                   |                 |               |                 |
| Autoimmune uveitis                              |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Keratitis                                       |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Vitreous haemorrhage                            |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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                      |                 |               |                 |
| Colitis   |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0         | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Constipation                                    |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Diarrhoea                                       |                 |               |                 |
| subjects affected / exposed                     | 3 / 223 (1.35%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 2 / 3           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Diverticulum                                    |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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           |

|   |                 |               |                 |
|---|-----------------|---------------|-----------------|
| Food poisoning                                  |                 |               |                 |
| subjects affected / exposed                     | 0 / 223 (0.00%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Gastritis                                       |                 |               |                 |
| subjects affected / exposed                     | 2 / 223 (0.90%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0         | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Haematemesis                                    |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Nausea  |                 |               |                 |
| subjects affected / exposed                     | 2 / 223 (0.90%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Oesophagitis                                    |                 |               |                 |
| subjects affected / exposed                     | 0 / 223 (0.00%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Proctitis                                       |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Vomiting  |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0         | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Hepatobiliary disorders                         |                 |               |                 |
| Cholecystitis                                   |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Hepatotoxicity                                  |                 |               |                 |

|   |                 |               |                 |
|---|-----------------|---------------|-----------------|
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Skin and subcutaneous tissue disorders          |                 |               |                 |
| Decubitus ulcer                                 |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Subacute cutaneous lupus erythematosus          |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Renal and urinary disorders                     |                 |               |                 |
| Acute kidney injury                             |                 |               |                 |
| subjects affected / exposed                     | 5 / 223 (2.24%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 4 / 7           | 0 / 0         | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Autoimmune nephritis                            |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Haematuria                                      |                 |               |                 |
| subjects affected / exposed                     | 0 / 223 (0.00%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Neurogenic bladder                              |                 |               |                 |
| subjects affected / exposed                     | 0 / 223 (0.00%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| 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                             |                 |               |                 |
| Hyperthyroidism                                 |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Inappropriate antidiuretic hormone secretion    |                 |               |                 |
| subjects affected / exposed                     | 2 / 223 (0.90%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Secondary adrenocortical insufficiency          |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Musculoskeletal and connective tissue disorders |                 |               |                 |
| Arthralgia                                      |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Back pain                                       |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Gouty arthritis                                 |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Myositis  |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Spinal osteoarthritis                           |                 |               |                 |



|   |                 |               |                 |
|---|-----------------|---------------|-----------------|
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| <b>Infections and infestations</b>              |                 |               |                 |
| <b>Appendicitis</b>                             |                 |               |                 |
| subjects affected / exposed                     | 0 / 223 (0.00%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| <b>Atypical pneumonia</b>                       |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| <b>Bacteraemia</b>                              |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0         | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| <b>Bronchitis</b>                               |                 |               |                 |
| subjects affected / exposed                     | 0 / 223 (0.00%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| <b>Cholecystitis infective</b>                  |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| <b>Clostridium difficile colitis</b>            |                 |               |                 |
| subjects affected / exposed                     | 2 / 223 (0.90%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| <b>Diverticulitis</b>                           |                 |               |                 |
| subjects affected / exposed                     | 0 / 223 (0.00%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 2 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| <b>Empyema</b>                                  |                 |               |                 |

|   |                 |               |                 |
|---|-----------------|---------------|-----------------|
| subjects affected / exposed                                   | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Escherichia sepsis  |                 |               |                 |
| subjects affected / exposed                                   | 0 / 223 (0.00%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 0         | 1 / 1           |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0         | 0 / 0           |
| Gastroenteritis   |                 |               |                 |
| subjects affected / exposed                                   | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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 viral infection                              |                 |               |                 |
| subjects affected / exposed                                   | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Herpes zoster   |                 |               |                 |
| subjects affected / exposed                                   | 0 / 223 (0.00%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all               | 0 / 0           | 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                                   | 0 / 223 (0.00%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 0         | 0 / 2           |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0         | 0 / 0           |
| Influenza   |                 |               |                 |
| subjects affected / exposed                                   | 0 / 223 (0.00%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0         | 0 / 0           |
| Lower respiratory tract infection                             |                 |               |                 |
| subjects affected / exposed                                   | 0 / 223 (0.00%) | 0 / 1 (0.00%) | 3 / 223 (1.35%) |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 0         | 1 / 3           |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0         | 0 / 0           |
| Neutropenic sepsis  |                 |               |                 |

|   |                  |               |                  |
|---|------------------|---------------|------------------|
| subjects affected / exposed                     | 3 / 223 (1.35%)  | 0 / 1 (0.00%) | 1 / 223 (0.45%)  |
| occurrences causally related to treatment / all | 3 / 3            | 0 / 0         | 1 / 1            |
| deaths causally related to treatment / all      | 3 / 3            | 0 / 0         | 1 / 1            |
| Paracancerous pneumonia                         |                  |               |                  |
| subjects affected / exposed                     | 1 / 223 (0.45%)  | 0 / 1 (0.00%) | 0 / 223 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0         | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0         | 0 / 0            |
| Pleural infection                               |                  |               |                  |
| subjects affected / exposed                     | 2 / 223 (0.90%)  | 0 / 1 (0.00%) | 0 / 223 (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            |
| Pneumonia                                       |                  |               |                  |
| subjects affected / exposed                     | 17 / 223 (7.62%) | 0 / 1 (0.00%) | 12 / 223 (5.38%) |
| occurrences causally related to treatment / all | 3 / 20           | 0 / 0         | 3 / 13           |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0         | 0 / 1            |
| Pneumonia haemophilus                           |                  |               |                  |
| subjects affected / exposed                     | 0 / 223 (0.00%)  | 0 / 1 (0.00%) | 1 / 223 (0.45%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0         | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0         | 0 / 0            |
| Pseudomonas infection                           |                  |               |                  |
| subjects affected / exposed                     | 1 / 223 (0.45%)  | 0 / 1 (0.00%) | 0 / 223 (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            |
| Sepsis  |                  |               |                  |
| subjects affected / exposed                     | 2 / 223 (0.90%)  | 0 / 1 (0.00%) | 0 / 223 (0.00%)  |
| occurrences causally related to treatment / all | 2 / 2            | 0 / 0         | 0 / 0            |
| deaths causally related to treatment / all      | 1 / 1            | 0 / 0         | 0 / 0            |
| Serratia sepsis                                 |                  |               |                  |
| subjects affected / exposed                     | 0 / 223 (0.00%)  | 0 / 1 (0.00%) | 1 / 223 (0.45%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0         | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0         | 0 / 0            |
| Tooth infection                                 |                  |               |                  |

|   |                 |               |                 |
|---|-----------------|---------------|-----------------|
| subjects affected / exposed                     | 0 / 223 (0.00%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Upper respiratory tract infection               |                 |               |                 |
| subjects affected / exposed                     | 0 / 223 (0.00%) | 0 / 1 (0.00%) | 3 / 223 (1.35%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Urinary tract infection                         |                 |               |                 |
| subjects affected / exposed                     | 3 / 223 (1.35%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Urosepsis                                       |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0         | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Pneumonia aspiration                            |                 |               |                 |
| subjects affected / exposed                     | 0 / 223 (0.00%) | 0 / 1 (0.00%) | 2 / 223 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 1           |
| Metabolism and nutrition disorders              |                 |               |                 |
| Decreased appetite                              |                 |               |                 |
| subjects affected / exposed                     | 0 / 223 (0.00%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Dehydration                                     |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 1 / 223 (0.45%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0         | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Diabetes mellitus                               |                 |               |                 |
| subjects affected / exposed                     | 2 / 223 (0.90%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Hyperglycaemia                                  |                 |               |                 |

|   |                 |               |                 |
|---|-----------------|---------------|-----------------|
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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           |
| Hyponatraemia                                   |                 |               |                 |
| subjects affected / exposed                     | 4 / 223 (1.79%) | 0 / 1 (0.00%) | 5 / 223 (2.24%) |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 0         | 0 / 11          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Type 1 diabetes mellitus                        |                 |               |                 |
| subjects affected / exposed                     | 1 / 223 (0.45%) | 0 / 1 (0.00%) | 0 / 223 (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           |

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

| <b>Non-serious adverse events</b>                     | Pembrolizumab+EP   | Pembrolizumab<br>Second Course | Placebo+EP         |
|---|--------------------|--------------------------------|--------------------|
| Total subjects affected by non-serious adverse events |                    |                                |                    |
| subjects affected / exposed                           | 221 / 223 (99.10%) | 1 / 1 (100.00%)                | 216 / 223 (96.86%) |
| Vascular disorders                                    |                    |                                |                    |
| Hypertension  |                    |                                |                    |
| subjects affected / exposed                           | 12 / 223 (5.38%)   | 0 / 1 (0.00%)                  | 10 / 223 (4.48%)   |
| occurrences (all)                                     | 15                 | 0                              | 14                 |
| Hypotension   |                    |                                |                    |
| subjects affected / exposed                           | 9 / 223 (4.04%)    | 0 / 1 (0.00%)                  | 16 / 223 (7.17%)   |
| occurrences (all)                                     | 11                 | 0                              | 21                 |
| General disorders and administration site conditions  |                    |                                |                    |
| Asthenia  |                    |                                |                    |
| subjects affected / exposed                           | 38 / 223 (17.04%)  | 0 / 1 (0.00%)                  | 43 / 223 (19.28%)  |
| occurrences (all)                                     | 46                 | 0                              | 48                 |
| Fatigue   |                    |                                |                    |
| subjects affected / exposed                           | 61 / 223 (27.35%)  | 0 / 1 (0.00%)                  | 60 / 223 (26.91%)  |
| occurrences (all)                                     | 76                 | 0                              | 78                 |
| Chest pain  |                    |                                |                    |
| subjects affected / exposed                           | 11 / 223 (4.93%)   | 0 / 1 (0.00%)                  | 21 / 223 (9.42%)   |
| occurrences (all)                                     | 11                 | 0                              | 24                 |
| Oedema peripheral                                     |                    |                                |                    |

|   |                   |               |                   |
|---|-------------------|---------------|-------------------|
| subjects affected / exposed                     | 17 / 223 (7.62%)  | 0 / 1 (0.00%) | 26 / 223 (11.66%) |
| occurrences (all)                               | 20                | 0             | 32                |
| Pyrexia   |                   |               |                   |
| subjects affected / exposed                     | 32 / 223 (14.35%) | 0 / 1 (0.00%) | 14 / 223 (6.28%)  |
| occurrences (all)                               | 37                | 0             | 17                |
| Respiratory, thoracic and mediastinal disorders |                   |               |                   |
| Cough   |                   |               |                   |
| subjects affected / exposed                     | 45 / 223 (20.18%) | 0 / 1 (0.00%) | 45 / 223 (20.18%) |
| occurrences (all)                               | 62                | 0             | 51                |
| Dyspnoea  |                   |               |                   |
| subjects affected / exposed                     | 37 / 223 (16.59%) | 0 / 1 (0.00%) | 37 / 223 (16.59%) |
| occurrences (all)                               | 41                | 0             | 41                |
| Psychiatric disorders                           |                   |               |                   |
| Insomnia  |                   |               |                   |
| subjects affected / exposed                     | 25 / 223 (11.21%) | 0 / 1 (0.00%) | 28 / 223 (12.56%) |
| occurrences (all)                               | 26                | 0             | 34                |
| Investigations                                  |                   |               |                   |
| Alanine aminotransferase increased              |                   |               |                   |
| subjects affected / exposed                     | 17 / 223 (7.62%)  | 0 / 1 (0.00%) | 21 / 223 (9.42%)  |
| occurrences (all)                               | 20                | 0             | 24                |
| Aspartate aminotransferase increased            |                   |               |                   |
| subjects affected / exposed                     | 19 / 223 (8.52%)  | 0 / 1 (0.00%) | 13 / 223 (5.83%)  |
| occurrences (all)                               | 22                | 0             | 15                |
| Blood creatinine increased                      |                   |               |                   |
| subjects affected / exposed                     | 15 / 223 (6.73%)  | 0 / 1 (0.00%) | 8 / 223 (3.59%)   |
| occurrences (all)                               | 23                | 0             | 8                 |
| Blood alkaline phosphatase increased            |                   |               |                   |
| subjects affected / exposed                     | 12 / 223 (5.38%)  | 0 / 1 (0.00%) | 6 / 223 (2.69%)   |
| occurrences (all)                               | 15                | 0             | 8                 |
| Weight decreased                                |                   |               |                   |
| subjects affected / exposed                     | 22 / 223 (9.87%)  | 0 / 1 (0.00%) | 20 / 223 (8.97%)  |
| occurrences (all)                               | 24                | 0             | 23                |
| Nervous system disorders                        |                   |               |                   |
| Dizziness                                       |                   |               |                   |
| subjects affected / exposed                     | 31 / 223 (13.90%) | 0 / 1 (0.00%) | 15 / 223 (6.73%)  |
| occurrences (all)                               | 36                | 0             | 17                |

|                                      |                    |               |                    |
|--------------------------------------|--------------------|---------------|--------------------|
| Headache                             |                    |               |                    |
| subjects affected / exposed          | 29 / 223 (13.00%)  | 0 / 1 (0.00%) | 34 / 223 (15.25%)  |
| occurrences (all)                    | 34                 | 0             | 41                 |
| Dysgeusia                            |                    |               |                    |
| subjects affected / exposed          | 14 / 223 (6.28%)   | 0 / 1 (0.00%) | 12 / 223 (5.38%)   |
| occurrences (all)                    | 14                 | 0             | 13                 |
| Blood and lymphatic system disorders |                    |               |                    |
| Anaemia                              |                    |               |                    |
| subjects affected / exposed          | 101 / 223 (45.29%) | 0 / 1 (0.00%) | 96 / 223 (43.05%)  |
| occurrences (all)                    | 122                | 0             | 115                |
| Leukopenia                           |                    |               |                    |
| subjects affected / exposed          | 49 / 223 (21.97%)  | 0 / 1 (0.00%) | 45 / 223 (20.18%)  |
| occurrences (all)                    | 84                 | 0             | 70                 |
| Neutropenia                          |                    |               |                    |
| subjects affected / exposed          | 120 / 223 (53.81%) | 0 / 1 (0.00%) | 114 / 223 (51.12%) |
| occurrences (all)                    | 217                | 0             | 207                |
| Thrombocytopenia                     |                    |               |                    |
| subjects affected / exposed          | 57 / 223 (25.56%)  | 0 / 1 (0.00%) | 46 / 223 (20.63%)  |
| occurrences (all)                    | 85                 | 0             | 80                 |
| Gastrointestinal disorders           |                    |               |                    |
| Abdominal pain                       |                    |               |                    |
| subjects affected / exposed          | 15 / 223 (6.73%)   | 0 / 1 (0.00%) | 13 / 223 (5.83%)   |
| occurrences (all)                    | 18                 | 0             | 13                 |
| Constipation                         |                    |               |                    |
| subjects affected / exposed          | 65 / 223 (29.15%)  | 0 / 1 (0.00%) | 59 / 223 (26.46%)  |
| occurrences (all)                    | 78                 | 0             | 69                 |
| Abdominal pain upper                 |                    |               |                    |
| subjects affected / exposed          | 13 / 223 (5.83%)   | 0 / 1 (0.00%) | 5 / 223 (2.24%)    |
| occurrences (all)                    | 14                 | 0             | 5                  |
| Dyspepsia                            |                    |               |                    |
| subjects affected / exposed          | 12 / 223 (5.38%)   | 0 / 1 (0.00%) | 7 / 223 (3.14%)    |
| occurrences (all)                    | 13                 | 0             | 7                  |
| Dysphagia                            |                    |               |                    |
| subjects affected / exposed          | 12 / 223 (5.38%)   | 0 / 1 (0.00%) | 6 / 223 (2.69%)    |
| occurrences (all)                    | 12                 | 0             | 6                  |
| Diarrhoea                            |                    |               |                    |

|  |                   |               |                   |
|--|-------------------|---------------|-------------------|
| subjects affected / exposed                  | 46 / 223 (20.63%) | 0 / 1 (0.00%) | 41 / 223 (18.39%) |
| occurrences (all)                            | 67                | 0             | 48                |
| Nausea                                       |                   |               |                   |
| subjects affected / exposed                  | 85 / 223 (38.12%) | 0 / 1 (0.00%) | 96 / 223 (43.05%) |
| occurrences (all)                            | 135               | 0             | 144               |
| Stomatitis                                   |                   |               |                   |
| subjects affected / exposed                  | 14 / 223 (6.28%)  | 0 / 1 (0.00%) | 15 / 223 (6.73%)  |
| occurrences (all)                            | 17                | 0             | 17                |
| Vomiting                                     |                   |               |                   |
| subjects affected / exposed                  | 36 / 223 (16.14%) | 0 / 1 (0.00%) | 39 / 223 (17.49%) |
| occurrences (all)                            | 48                | 0             | 49                |
| Skin and subcutaneous tissue disorders       |                   |               |                   |
| Alopecia                                     |                   |               |                   |
| subjects affected / exposed                  | 75 / 223 (33.63%) | 0 / 1 (0.00%) | 84 / 223 (37.67%) |
| occurrences (all)                            | 77                | 0             | 87                |
| Dry skin                                     |                   |               |                   |
| subjects affected / exposed                  | 13 / 223 (5.83%)  | 0 / 1 (0.00%) | 10 / 223 (4.48%)  |
| occurrences (all)                            | 13                | 0             | 10                |
| Erythema                                     |                   |               |                   |
| subjects affected / exposed                  | 13 / 223 (5.83%)  | 0 / 1 (0.00%) | 4 / 223 (1.79%)   |
| occurrences (all)                            | 14                | 0             | 4                 |
| Pruritus                                     |                   |               |                   |
| subjects affected / exposed                  | 25 / 223 (11.21%) | 0 / 1 (0.00%) | 18 / 223 (8.07%)  |
| occurrences (all)                            | 33                | 0             | 23                |
| Rash   |                   |               |                   |
| subjects affected / exposed                  | 30 / 223 (13.45%) | 0 / 1 (0.00%) | 13 / 223 (5.83%)  |
| occurrences (all)                            | 39                | 0             | 17                |
| Endocrine disorders                          |                   |               |                   |
| Hyperthyroidism                              |                   |               |                   |
| subjects affected / exposed                  | 12 / 223 (5.38%)  | 0 / 1 (0.00%) | 6 / 223 (2.69%)   |
| occurrences (all)                            | 12                | 0             | 7                 |
| Hypothyroidism                               |                   |               |                   |
| subjects affected / exposed                  | 26 / 223 (11.66%) | 0 / 1 (0.00%) | 5 / 223 (2.24%)   |
| occurrences (all)                            | 27                | 0             | 5                 |
| Inappropriate antidiuretic hormone secretion |                   |               |                   |



|  |                      |                      |                      |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all) | 1 / 223 (0.45%)<br>1 | 1 / 1 (100.00%)<br>1 | 1 / 223 (0.45%)<br>1 |
| Musculoskeletal and connective tissue disorders  |                      |                      |                      |
| Arthralgia                                       |                      |                      |                      |
| subjects affected / exposed                      | 29 / 223 (13.00%)    | 0 / 1 (0.00%)        | 19 / 223 (8.52%)     |
| occurrences (all)                                | 37                   | 0                    | 22                   |
| Back pain  |                      |                      |                      |
| subjects affected / exposed                      | 25 / 223 (11.21%)    | 0 / 1 (0.00%)        | 26 / 223 (11.66%)    |
| occurrences (all)                                | 27                   | 0                    | 27                   |
| Pain in extremity                                |                      |                      |                      |
| subjects affected / exposed                      | 12 / 223 (5.38%)     | 0 / 1 (0.00%)        | 13 / 223 (5.83%)     |
| occurrences (all)                                | 15                   | 0                    | 16                   |
| Musculoskeletal chest pain                       |                      |                      |                      |
| subjects affected / exposed                      | 12 / 223 (5.38%)     | 0 / 1 (0.00%)        | 6 / 223 (2.69%)      |
| occurrences (all)                                | 14                   | 0                    | 6                    |
| Infections and infestations                      |                      |                      |                      |
| Pneumonia  |                      |                      |                      |
| subjects affected / exposed                      | 12 / 223 (5.38%)     | 0 / 1 (0.00%)        | 13 / 223 (5.83%)     |
| occurrences (all)                                | 13                   | 0                    | 14                   |
| Upper respiratory tract infection                |                      |                      |                      |
| subjects affected / exposed                      | 17 / 223 (7.62%)     | 0 / 1 (0.00%)        | 13 / 223 (5.83%)     |
| occurrences (all)                                | 22                   | 0                    | 16                   |
| Nasopharyngitis                                  |                      |                      |                      |
| subjects affected / exposed                      | 12 / 223 (5.38%)     | 0 / 1 (0.00%)        | 9 / 223 (4.04%)      |
| occurrences (all)                                | 15                   | 0                    | 9                    |
| Urinary tract infection                          |                      |                      |                      |
| subjects affected / exposed                      | 10 / 223 (4.48%)     | 1 / 1 (100.00%)      | 8 / 223 (3.59%)      |
| occurrences (all)                                | 12                   | 1                    | 9                    |
| Metabolism and nutrition disorders               |                      |                      |                      |
| Decreased appetite                               |                      |                      |                      |
| subjects affected / exposed                      | 69 / 223 (30.94%)    | 0 / 1 (0.00%)        | 54 / 223 (24.22%)    |
| occurrences (all)                                | 85                   | 0                    | 68                   |
| Hypokalaemia                                     |                      |                      |                      |
| subjects affected / exposed                      | 15 / 223 (6.73%)     | 0 / 1 (0.00%)        | 13 / 223 (5.83%)     |
| occurrences (all)                                | 20                   | 0                    | 19                   |
| Hyponatraemia                                    |                      |                      |                      |

|                             |                  |               |                  |
|-----------------------------|------------------|---------------|------------------|
| subjects affected / exposed | 21 / 223 (9.42%) | 0 / 1 (0.00%) | 16 / 223 (7.17%) |
| occurrences (all)           | 26               | 0             | 23               |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment  |
|-------------------|--|
| 11 January 2017   | Amendment 1 corrected a typographical error in the numbering of the inclusion criteria.  |
| 14 March 2017     | Amendment 2 corrected the timeframe associated with the exclusion criterion for major surgery.   |
| 17 April 2017     | Amendment 3 removed the option to crossover from the placebo+etoposide+platinum arm to pembrolizumab treatment after documentation of progressive disease.   |
| 06 July 2017      | Amendment 4 removed the requirement for unblinding treatment assignment after documentation of progressive disease because the option to cross over to pembrolizumab was removed and, with it, the need to unblind.  |
| 11 September 2017 | Amendment 5 clarified the exclusion criterion regarding study participation for participants with brain metastases.  |
| 21 December 2017  | Amendment 6 updated the dose modification guidelines for pembrolizumab to include information regarding the treatment of myocarditis, revised the requirements for survival follow-up to allow for more frequent data collection, and added a Day 8 visit during Cycles 1 through 4 to allow for more frequent safety monitoring.  |
| 06 November 2018  | Amendment 7 updated criteria for the first and second interim analyses to calendar time from the time the first patient was randomized to ensure sufficient follow-up time for PFS analyses and manage the gap between the first two interim analysis, changed the alpha spending strategy for PFS to calendar time to align with the interim analyses, and changed the alpha allocation between the primary (OS and PFS) and key secondary (ORR) hypothesis on the basis of accumulating external data on PFS and OS in immunotherapy-chemotherapy combinations in small cell lung cancer to allow more alpha to be allocated to the primary endpoints. |
| 15 January 2019   | Amendment 8 changed the alpha spending function for PFS analysis from Hwang Shih DeCani to Lan-DeMets O'Brien Fleming, the alpha spending approach was changed from time-based to information fraction-based spending, the assumption for median PFS in the control arm was changed to 4.3 months based on external data published from other clinical trials, and the power and efficacy bound calculations were updated to reflect the change in PFS median assumption and an alpha spending approach.   |
| 24 May 2019       | Amendment 9 updated criteria for the final OS analysis to be a minimum of 294 events, or 31 months from study start, whichever occurs later to ensure sufficient follow-up time for the final OS analysis, added clarification to describe the alpha-spending strategy for PFS and OS in detail, and corrected a publishing error in Amendment 08.   |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported