

**Clinical trial results:****A Randomized Open-Label Phase III Trial of Pembrolizumab versus Platinum based Chemotherapy in 1L Subjects with PD-L1 Strong Metastatic Non-Small Cell Lung Cancer****Summary**

|                          |                            |
|--------------------------|----------------------------|
| EudraCT number           | 2014-000323-25             |
| Trial protocol           | IT IE HU DE ES BE NL FR AT |
| Global end of trial date | 27 May 2021                |

**Results information**

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 03 June 2022 |
| First version publication date | 03 June 2022 |

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

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 3475-024 |
|-----------------------|----------|

**Additional study identifiers**

|                                    |               |
|------------------------------------|---------------|
| ISRCTN number                      | -             |
| ClinicalTrials.gov id (NCT number) | NCT02142738   |
| WHO universal trial number (UTN)   | -             |
| Other trial identifiers            | JAPIC: 142728 |

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,<br>ClinicalTrialsDisclosure@merck.com |
| Scientific contact           | Clinical Trials Disclosure, Merck Sharp & Dohme LLC,<br>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                       | 27 May 2021 |
| Is this the analysis of the primary completion data? | No          |
| Global end of trial reached?                         | Yes         |
| Global end of trial date                             | 27 May 2021 |
| Was the trial ended prematurely?                     | No          |

Notes:

## General information about the trial

Main objective of the trial:

This is a study to assess the efficacy and safety of pembrolizumab (MK-3475/SCH 900475) compared to standard of care (SOC) platinum-based chemotherapies in the treatment of participants with previously untreated stage IV, programmed cell death ligand 1 (PD-L1) strong expressing Non-Small Cell Lung Cancer (NSCLC). The primary hypothesis of this study is that participants with PD-L1 strong NSCLC will have a longer Progression Free Survival (PFS), as assessed by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) when treated with pembrolizumab than when treated with SOC platinum-based chemotherapies.

With Amendment 09 (20 December 2017), once participants have achieved the study objective or the study has ended, participants will be discontinued from this study and enrolled in an extension study to continue protocol-defined assessments and treatment.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

|   |                |
|---|----------------|
| Actual start date of recruitment                          | 25 August 2014 |
| Long term follow-up planned                               | No             |
| Independent data monitoring committee (IDMC) involvement? | Yes            |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                |
|--------------------------------------|----------------|
| Country: Number of subjects enrolled | Australia: 21  |
| Country: Number of subjects enrolled | Austria: 4     |
| Country: Number of subjects enrolled | Belgium: 5     |
| Country: Number of subjects enrolled | Canada: 15     |
| Country: Number of subjects enrolled | France: 11     |
| Country: Number of subjects enrolled | Germany: 23    |
| Country: Number of subjects enrolled | Hungary: 28    |
| Country: Number of subjects enrolled | Ireland: 8     |
| Country: Number of subjects enrolled | Israel: 28     |
| Country: Number of subjects enrolled | Italy: 21      |
| Country: Number of subjects enrolled | Japan: 40      |
| Country: Number of subjects enrolled | Netherlands: 4 |
| Country: Number of subjects enrolled | New Zealand: 2 |
| Country: Number of subjects enrolled | Spain: 33      |

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 21 |
| Country: Number of subjects enrolled | United States: 41  |
| Worldwide total number of subjects   | 305                |
| EEA total number of subjects         | 137                |

Notes:

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**Subjects enrolled per age group**

|   |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 141 |
| From 65 to 84 years                       | 159 |
| 85 years and over                         | 5   |

## Subject disposition

### Recruitment

Recruitment details:

Participants with Non-Small Cell Lung Cancer (NSCLC) were enrolled in this study.

### Pre-assignment

Screening details:

Per protocol, it was planned that participants would be randomized 1:1 to receive either pembrolizumab or investigator-choice standard of care (SOC) chemotherapy and data analysis would be conducted on the two treatment arms: Pembrolizumab and SOC Chemotherapy.

### Period 1

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

### Arms

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

Arm description:

Participants received pembrolizumab 200 mg, administered as intravenous (IV) infusion on Day 1 of each 21-day cycle for up to 35 cycles or until documented progressive disease (PD) or participant discontinuation.

|  |                              |
|--|------------------------------|
| Arm type                               | Experimental                 |
| Investigational medicinal product name | Pembrolizumab                |
| Investigational medicinal product code |                              |
| Other name                             | KEYTRUDA® MK-3475 SCH 900475 |
| Pharmaceutical forms                   | Infusion                     |
| Routes of administration               | Intravenous use              |

Dosage and administration details:

200 mg Every 3 Weeks (Q3W)

|                  |                  |
|------------------|------------------|
| <b>Arm title</b> | SOC Chemotherapy |
|------------------|------------------|

Arm description:

Participants received 1 of 5 possible standard chemotherapy regimens at the investigator's discretion by IV infusion administered on 21-day cycles for 4-6 cycles or until progressive disease or participant discontinuation: paclitaxel 200 mg/m<sup>2</sup> and carboplatin Area Under the Curve (AUC) 5 or 6 on Day 1 of each cycle; pemetrexed 500 mg/m<sup>2</sup> and carboplatin AUC 5 or 6 on Day 1 of each cycle; pemetrexed 500 mg/m<sup>2</sup> and cisplatin 75 mg/m<sup>2</sup> on Day 1 of each cycle; gemcitabine 1250 mg/m<sup>2</sup> on Days 1 and 8 of each cycle and carboplatin AUC 5 or 6 on Day 1 of a cycle or gemcitabine 1250 mg/m<sup>2</sup> on Days 1 and 8 of each cycle and cisplatin 75 mg/m<sup>2</sup> on Day 1 of each cycle. Participants with PD following chemotherapy can switch to pembrolizumab for up to 35 cycles. Participants who switched to and then stopped pembrolizumab and had stable disease but progressed after discontinuation, initiate a second course of pembrolizumab at the investigator's discretion for up to 17 cycles.

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

Dosage and administration details:

200 mg/m<sup>2</sup> Q3W

|   |                     |
|---|---------------------|
| Investigational medicinal product name                      | Carboplatin         |
| Investigational medicinal product code                      |                     |
| Other name  |                     |
| Pharmaceutical forms  | Infusion            |
| Routes of administration                                    | Intravenous use     |
| Dosage and administration details:                          |                     |
| Area Under the Curve (AUC) 5 or 6 Q3W                       |                     |
| Investigational medicinal product name                      | Cisplatin           |
| Investigational medicinal product code                      |                     |
| Other name  |                     |
| Pharmaceutical forms  | Infusion            |
| Routes of administration                                    | Intravenous use     |
| Dosage and administration details:                          |                     |
| 75 mg/m <sup>2</sup> Q3W                                    |                     |
| Investigational medicinal product name                      | Pemetrexed          |
| Investigational medicinal product code                      |                     |
| Other name  |                     |
| Pharmaceutical forms  | Powder for infusion |
| Routes of administration                                    | Intravenous use     |
| Dosage and administration details:                          |                     |
| 500 mg/m <sup>2</sup> Q3W                                   |                     |
| Investigational medicinal product name                      | Gemcitabine         |
| Investigational medicinal product code                      |                     |
| Other name  |                     |
| Pharmaceutical forms  | Powder for infusion |
| Routes of administration                                    | Intravascular use   |
| Dosage and administration details:                          |                     |
| 1250 mg/m <sup>2</sup> on Days 1 and 8 of each 21-day cycle |                     |

| <b>Number of subjects in period 1</b> | Pembrolizumab | SOC Chemotherapy |
|---------------------------------------|---------------|------------------|
| Started                               | 154           | 151              |
| Treated                               | 154           | 150              |
| Chemotherapy Switch to Pembrolizumab  | 0             | 83               |
| Second Course Pembrolizumab           | 12            | 1                |
| Completed                             | 0             | 0                |
| Not completed                         | 154           | 151              |
| Adverse event, serious fatal          | 92            | 112              |
| Consent withdrawn by subject          | 6             | 7                |
| Adverse event, non-fatal              | 13            | 9                |
| Follow up ended by sponsor            | 43            | 20               |
| Lost to follow-up                     | -             | 3                |



## Baseline characteristics

### Reporting groups

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

Reporting group description:

Participants received pembrolizumab 200 mg, administered as intravenous (IV) infusion on Day 1 of each 21-day cycle for up to 35 cycles or until documented progressive disease (PD) or participant discontinuation.

|                       |                  |
|-----------------------|------------------|
| Reporting group title | SOC Chemotherapy |
|-----------------------|------------------|

Reporting group description:

Participants received 1 of 5 possible standard chemotherapy regimens at the investigator's discretion by IV infusion administered on 21-day cycles for 4-6 cycles or until progressive disease or participant discontinuation: paclitaxel 200 mg/m<sup>2</sup> and carboplatin Area Under the Curve (AUC) 5 or 6 on Day 1 of each cycle; pemetrexed 500 mg/m<sup>2</sup> and carboplatin AUC 5 or 6 on Day 1 of each cycle; pemetrexed 500 mg/m<sup>2</sup> and cisplatin 75 mg/m<sup>2</sup> on Day 1 of each cycle; gemcitabine 1250 mg/m<sup>2</sup> on Days 1 and 8 of each cycle and carboplatin AUC 5 or 6 on Day 1 of a cycle or gemcitabine 1250 mg/m<sup>2</sup> on Days 1 and 8 of each cycle and cisplatin 75 mg/m<sup>2</sup> on Day 1 of each cycle. Participants with PD following chemotherapy can switch to pembrolizumab for up to 35 cycles. Participants who switched to and then stopped pembrolizumab and had stable disease but progressed after discontinuation, initiate a second course of pembrolizumab at the investigator's discretion for up to 17 cycles.

| Reporting group values                             | Pembrolizumab | SOC Chemotherapy | Total |
|--|---------------|------------------|-------|
| Number of subjects                                 | 154           | 151              | 305   |
| Age categorical                                    |               |                  |       |
| Units: Participants                                |               |                  |       |
| 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)                               | 77            | 64               | 141   |
| From 65-84 years                                   | 74            | 85               | 159   |
| 85 years and over                                  | 3             | 2                | 5     |
| Age Continuous                                     |               |                  |       |
| Units: Years                                       |               |                  |       |
| arithmetic mean                                    | 63.9          | 64.6             | -     |
| standard deviation                                 | ± 10.1        | ± 9.5            | -     |
| Sex: Female, Male                                  |               |                  |       |
| Units: Participants                                |               |                  |       |
| Female   | 62            | 56               | 118   |
| Male   | 92            | 95               | 187   |
| Race (NIH/OMB)                                     |               |                  |       |
| Units: Subjects                                    |               |                  |       |
| American Indian or Alaska Native                   | 0             | 1                | 1     |
| Asian  | 25            | 21               | 46    |
| Native Hawaiian or Other Pacific Islander          | 0             | 1                | 1     |
| Black or African American                          | 2             | 2                | 4     |
| White  | 125           | 126              | 251   |
| More than one race                                 | 0             | 0                | 0     |

|  |     |     |     |
|--|-----|-----|-----|
| Unknown or Not Reported  | 2   | 0   | 2   |
| Ethnicity (NIH/OMB)  |     |     |     |
| Units: Subjects  |     |     |     |
| Hispanic or Latino   | 1   | 5   | 6   |
| Not Hispanic or Latino   | 148 | 135 | 283 |
| Unknown or Not Reported  | 5   | 11  | 16  |
| Eastern Cooperative Oncology Group (ECOG) Status (0, 1 or 2)   |     |     |     |
| Eastern Cooperative Oncology Group (ECOG) Performance. ECOG is presented where 0 = Fully active, no performance restrictions; 1 = Strenuous physical activity restricted, fully ambulatory & able to carry out light work; and 2 = In bed <50% of the time, ambulatory and capable of all self-care, but unable to carry out any work activities |     |     |     |
| Units: Subjects  |     |     |     |
| ECOG = 0   | 54  | 53  | 107 |
| ECOG = 1   | 99  | 98  | 197 |
| ECOG = 2   | 1   | 0   | 1   |
| Histology  |     |     |     |
| Participants were categorized according to the histology of their carcinoma  |     |     |     |
| Units: Subjects  |     |     |     |
| ADENOCARCINOMA   | 104 | 108 | 212 |
| ADENOSQUAMOUS  | 2   | 2   | 4   |
| LARGE CELL CARCINOMA   | 2   | 2   | 4   |
| NON-SQUAMOUS CELL CARCINOMA  | 5   | 7   | 12  |
| POORLY DIFFERENTIATED  | 9   | 3   | 12  |
| SARCOMATOID  | 3   | 2   | 5   |
| SQUAMOUS CELL CARCINOMA  | 29  | 26  | 55  |
| POORLY DIFFERENTIATED SQUAMOUS CELL CARCINOMA  | 0   | 1   | 1   |
| Geographic Region of Enrolling Site  |     |     |     |
| Units: Subjects  |     |     |     |
| Non-East Asia  | 133 | 132 | 265 |
| East Asia  | 21  | 19  | 40  |

## End points

### End points reporting groups

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

Reporting group description:

Participants received pembrolizumab 200 mg, administered as intravenous (IV) infusion on Day 1 of each 21-day cycle for up to 35 cycles or until documented progressive disease (PD) or participant discontinuation.

|                       |                  |
|-----------------------|------------------|
| Reporting group title | SOC Chemotherapy |
|-----------------------|------------------|

Reporting group description:

Participants received 1 of 5 possible standard chemotherapy regimens at the investigator's discretion by IV infusion administered on 21-day cycles for 4-6 cycles or until progressive disease or participant discontinuation: paclitaxel 200 mg/m<sup>2</sup> and carboplatin Area Under the Curve (AUC) 5 or 6 on Day 1 of each cycle; pemetrexed 500 mg/m<sup>2</sup> and carboplatin AUC 5 or 6 on Day 1 of each cycle; pemetrexed 500 mg/m<sup>2</sup> and cisplatin 75 mg/m<sup>2</sup> on Day 1 of each cycle; gemcitabine 1250 mg/m<sup>2</sup> on Days 1 and 8 of each cycle and carboplatin AUC 5 or 6 on Day 1 of a cycle or gemcitabine 1250 mg/m<sup>2</sup> on Days 1 and 8 of each cycle and cisplatin 75 mg/m<sup>2</sup> on Day 1 of each cycle. Participants with PD following chemotherapy can switch to pembrolizumab for up to 35 cycles. Participants who switched to and then stopped pembrolizumab and had stable disease but progressed after discontinuation, initiate a second course of pembrolizumab at the investigator's discretion for up to 17 cycles.

### Primary: Progression Free Survival (PFS) Rate at Month 6

|                 |   |
|-----------------|---|
| End point title | Progression Free Survival (PFS) Rate at Month 6 |
|-----------------|---|

End point description:

PFS was defined as the time from randomization to documented disease progression per RECIST 1.1 or death due to any cause, whichever occurred first and was based on blinded independent central radiologists' (BICR) review. Progressive Disease (PD) was defined as  $\geq 20\%$  increase in the sum of diameters of target lesions and an absolute increase of  $\geq 5$  mm. (Note: the appearance of one or more new lesions was also considered progression). Participants were evaluated every 9 weeks with radiographic imaging to assess their response to treatment. The data cutoff date was 09-May-2016. The PFS rate at Month 6 was calculated. The Intention-to-treat (ITT) population included all randomized participants. Participants were included in the treatment group to which they were randomized, regardless of whether or not they received study treatment.

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

End point timeframe:

Month 6

| End point values                  | Pembrolizumab       | SOC Chemotherapy    |  |  |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type                | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed       | 154                 | 151                 |  |  |
| Units: Percentage of Participants |                     |                     |  |  |
| number (confidence interval 95%)  | 62.1 (53.8 to 69.4) | 50.3 (41.9 to 58.2) |  |  |

### Statistical analyses

|                            |   |
|----------------------------|---|
| Statistical analysis title | Superiority of Pembrolizumab versus SOC |
|----------------------------|---|

Statistical analysis description:

Treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. nonsquamous).

|   |                                  |
|---|----------------------------------|
| Comparison groups                       | Pembrolizumab v SOC Chemotherapy |
| Number of subjects included in analysis | 305                              |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           | superiority                      |
| P-value                                 | < 0.001 [1]                      |
| Method                                  | Regression, Cox                  |
| Parameter estimate                      | Hazard ratio (HR)                |
| Point estimate                          | 0.5                              |
| Confidence interval                     |                                  |
| level                                   | 95 %                             |
| sides                                   | 2-sided                          |
| lower limit                             | 0.37                             |
| upper limit                             | 0.68                             |

Notes:

[1] - One-sided p-value based on log-rank test

### Secondary: Overall Survival (OS) Rate

|  |                            |
|--|----------------------------|
| End point title  | Overall Survival (OS) Rate |
| 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 data cutoff date was 10-July-2017. The median OS rate is presented for month 12. The ITT population included all randomized participants. Participants were included in the treatment group to which they were randomized, regardless of whether or not they received study treatment. |                            |
| End point type   | Secondary                  |
| End point timeframe:   |                            |
| 12 months  |                            |

| End point values                  | Pembrolizumab       | SOC Chemotherapy    |  |  |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type                | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed       | 154                 | 151                 |  |  |
| Units: Percentage of Participants |                     |                     |  |  |
| number (confidence interval 95%)  | 70.3 (62.3 to 76.9) | 54.8 (46.4 to 62.4) |  |  |

### Statistical analyses

|   |                                     |
|---|-------------------------------------|
| <b>Statistical analysis title</b>   | Superiority of Pembrolizumab to SOC |
| Statistical analysis description:   |                                     |
| Treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. nonsquamous). |                                     |
| Comparison groups   | Pembrolizumab v SOC Chemotherapy    |

|   |                   |
|---|-------------------|
| Number of subjects included in analysis | 305               |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | superiority       |
| P-value                                 | = 0.002 [2]       |
| Method                                  | Regression, Cox   |
| Parameter estimate                      | Hazard ratio (HR) |
| Point estimate                          | 0.63              |
| Confidence interval                     |                   |
| level                                   | 95 %              |
| sides                                   | 2-sided           |
| lower limit                             | 0.47              |
| upper limit                             | 0.86              |

Notes:

[2] - One-sided p-value based on log-rank test

### Secondary: Objective Response Rate (ORR)

|  |                               |
|--|-------------------------------|
| End point title  | Objective Response Rate (ORR) |
| End point description:   |                               |
| <p>ORR was defined as the percentage of participants in the analysis population who experienced a Complete Response (CR; disappearance of all target lesions) or a Partial Response (PR; at least a 30% decrease in the sum of diameters of target lesions) and was assessed using RECIST 1.1 based on BICR evaluation. ORR was assessed from enrollment/treatment initiation of a participant through data cutoff date of 09-May-2016. The Intention-to-treat (ITT) population included all randomized participants. Participants were included in the treatment group to which they were randomized, regardless of whether or not they received study treatment.</p> |                               |
| End point type   | Secondary                     |
| End point timeframe:   |                               |
| Up to approximately 1.6 years  |                               |

| End point values                  | Pembrolizumab       | SOC<br>Chemotherapy |  |  |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type                | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed       | 154                 | 151                 |  |  |
| Units: Percentage of Participants |                     |                     |  |  |
| number (confidence interval 95%)  | 44.8 (36.8 to 53.0) | 27.8 (20.8 to 35.7) |  |  |

### Statistical analyses

|  |   |
|--|---|
| Statistical analysis title   | Superiority of Pembrolizumab versus SOC |
| Statistical analysis description:  |   |
| <p>Treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. nonsquamous).</p> |   |
| Comparison groups  | Pembrolizumab v SOC Chemotherapy        |

|   |                             |
|---|-----------------------------|
| Number of subjects included in analysis | 305                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority                 |
| P-value                                 | = 0.0011 <sup>[3]</sup>     |
| Method                                  | Miettinen & Nurminen method |
| Parameter estimate                      | Difference in percentages   |
| Point estimate                          | 16.6                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 6                           |
| upper limit                             | 27                          |

Notes:

[3] - One-sided p-value for testing

## Adverse events

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### Adverse events information

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Timeframe for reporting adverse events:

Up to approximately 80 months.

Adverse event reporting additional description:

Deaths: All randomized participants (the number at risk for SOC Chemotherapy first course is 151).  
Safety: All randomized participants who got  $\geq 1$  dose of study drug. Per protocol MedDRA preferred terms "Neoplasm progression" and "Malignant neoplasm progression" not related to study drug are excluded as AEs.

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

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### Dictionary used

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

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|                    |      |
|--------------------|------|
| Dictionary version | 23.1 |
|--------------------|------|

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### Reporting groups

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

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Reporting group description:

Participants received pembrolizumab 200 mg, administered as intravenous (IV) infusion on Day 1 of each 21-day cycle for up to 35 cycles or until documented progressive disease (PD) or participant discontinuation.

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|                       |                               |
|-----------------------|-------------------------------|
| Reporting group title | SOC Chemotherapy First Course |
|-----------------------|-------------------------------|

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Reporting group description:

Participants received 1 of 5 possible standard chemotherapy regimens at the investigator's discretion by IV infusion administered on 21-day cycles for 4-6 cycles or until progressive disease or participant discontinuation: paclitaxel 200 mg/m<sup>2</sup> and carboplatin Area Under the Curve (AUC) 5 or 6 on Day 1 of each cycle; pemetrexed 500 mg/m<sup>2</sup> and carboplatin AUC 5 or 6 on Day 1 of each cycle; pemetrexed 500 mg/m<sup>2</sup> and cisplatin 75 mg/m<sup>2</sup> on Day 1 of each cycle; gemcitabine 1250 mg/m<sup>2</sup> on Days 1 and 8 of each cycle and carboplatin AUC 5 or 6 on Day 1 of a cycle or gemcitabine 1250 mg/m<sup>2</sup> on Days 1 and 8 of each cycle and cisplatin 75 mg/m<sup>2</sup> on Day 1 of each cycle. Participants with PD following chemotherapy can switch to pembrolizumab for up to 35 cycles. Participants who switched to and then stopped pembrolizumab and had stable disease but progressed after discontinuation, initiate a second course of pembrolizumab at the investigator's discretion for up to 17 cycles.

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|                       |  |
|-----------------------|--|
| Reporting group title | SOC Chemotherapy Switched over to Second Course<br>Pembrolizumab |
|-----------------------|--|

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Reporting group description:

One qualified participant received SOC chemotherapy first course, but continued to experience disease progression and at investigator's discretion switched to a course of pembrolizumab IV 200 mg, every cycle (three weeks) for up to 35 cycles up to ~2 years. The participant then initiated a second course of pembrolizumab at the same dose and schedule for up to ~1 additional year until documented PD or participant discontinuation.

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

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Reporting group description:

Qualified participants who received the pembrolizumab first course and achieved CR, PR, or stable disease, and progressed after discontinuation, at the investigator's discretion, initiated a second course of pembrolizumab at the same dose and schedule for up to 17 cycles (approximately 1 additional year).

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|                       |  |
|-----------------------|--|
| Reporting group title | SOC Chemotherapy Switched Over to Pembrolizumab First Course |
|-----------------------|--|

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Reporting group description:

Qualified participants who received the SOC chemotherapy first course but continued to experience disease progression, at the investigator's discretion, initiated a course of pembrolizumab IV 200 mg, every cycle (three weeks) for up to 35 cycles up to ~2 years.

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| <b>Serious adverse events</b>                                       | <b>Pembrolizumab First Course</b> | <b>SOC Chemotherapy First Course</b> | <b>SOC Chemotherapy Switched over to Second Course Pembrolizumab</b> |
|---|-----------------------------------|--------------------------------------|--|
| Total subjects affected by serious adverse events                   |                                   |                                      |  |
| subjects affected / exposed   | 79 / 154 (51.30%)                 | 70 / 150 (46.67%)                    | 0 / 1 (0.00%)  |
| number of deaths (all causes)                                       | 103                               | 60                                   | 1  |
| number of deaths resulting from adverse events                      | 2                                 | 3                                    | 0  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                   |                                      |  |
| Bladder neoplasm  |                                   |                                      |  |
| subjects affected / exposed   | 0 / 154 (0.00%)                   | 1 / 150 (0.67%)                      | 0 / 1 (0.00%)  |
| occurrences causally related to treatment / all                     | 0 / 0                             | 0 / 1                                | 0 / 0  |
| deaths causally related to treatment / all                          | 0 / 0                             | 0 / 0                                | 0 / 0  |
| Cancer pain   |                                   |                                      |  |
| subjects affected / exposed   | 0 / 154 (0.00%)                   | 1 / 150 (0.67%)                      | 0 / 1 (0.00%)  |
| occurrences causally related to treatment / all                     | 0 / 0                             | 0 / 1                                | 0 / 0  |
| deaths causally related to treatment / all                          | 0 / 0                             | 0 / 0                                | 0 / 0  |
| Infected neoplasm   |                                   |                                      |  |
| subjects affected / exposed   | 1 / 154 (0.65%)                   | 0 / 150 (0.00%)                      | 0 / 1 (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  |
| Malignant neoplasm progression                                      |                                   |                                      |  |
| subjects affected / exposed   | 0 / 154 (0.00%)                   | 1 / 150 (0.67%)                      | 0 / 1 (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  |
| Appendix cancer   |                                   |                                      |  |
| subjects affected / exposed   | 1 / 154 (0.65%)                   | 0 / 150 (0.00%)                      | 0 / 1 (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  |
| Bladder cancer  |                                   |                                      |  |
| subjects affected / exposed   | 0 / 154 (0.00%)                   | 0 / 150 (0.00%)                      | 0 / 1 (0.00%)  |
| occurrences causally related to treatment / all                     | 0 / 0                             | 0 / 0                                | 0 / 0  |
| deaths causally related to treatment / all                          | 0 / 0                             | 0 / 0                                | 0 / 0  |
| Bladder transitional cell carcinoma                                 |                                   |                                      |  |

|  |                 |                 |               |
|--|-----------------|-----------------|---------------|
| subjects affected / exposed                          | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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         |
| Colon cancer   |                 |                 |               |
| subjects affected / exposed                          | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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         |
| Colorectal adenocarcinoma                            |                 |                 |               |
| subjects affected / exposed                          | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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                                   |                 |                 |               |
| Vasospasm  |                 |                 |               |
| subjects affected / exposed                          | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 1 (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         |
| Embolism   |                 |                 |               |
| subjects affected / exposed                          | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0         |
| Ischaemia  |                 |                 |               |
| subjects affected / exposed                          | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0         |
| Superior vena cava occlusion                         |                 |                 |               |
| subjects affected / exposed                          | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0         |
| General disorders and administration site conditions |                 |                 |               |
| Chest pain   |                 |                 |               |
| subjects affected / exposed                          | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0         |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| Death   |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 2 / 150 (1.33%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 2           | 0 / 0         |
| Face oedema                                     |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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         |
| Fatigue   |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 1 / 150 (0.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Gait disturbance                                |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 1 (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         |
| General physical health deterioration           |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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         |
| Multiple organ dysfunction syndrome             |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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         |
| Oedema peripheral                               |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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         |
| Pyrexia   |                 |                 |               |
| subjects affected / exposed                     | 2 / 154 (1.30%) | 1 / 150 (0.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 1 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Sudden death                                    |                 |                 |               |

|  |                 |                 |               |
|--|-----------------|-----------------|---------------|
| subjects affected / exposed                            | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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         |
| <b>Immune system disorders</b>                         |                 |                 |               |
| <b>Anaphylactic shock</b>                              |                 |                 |               |
| subjects affected / exposed                            | 2 / 154 (1.30%) | 0 / 150 (0.00%) | 0 / 1 (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         |
| <b>Hypersensitivity</b>                                |                 |                 |               |
| subjects affected / exposed                            | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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>Anaphylactic reaction</b>                           |                 |                 |               |
| subjects affected / exposed                            | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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>Reproductive system and breast disorders</b>        |                 |                 |               |
| <b>Ovarian haemorrhage</b>                             |                 |                 |               |
| subjects affected / exposed                            | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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>Respiratory, thoracic and mediastinal disorders</b> |                 |                 |               |
| <b>Acute respiratory failure</b>                       |                 |                 |               |
| subjects affected / exposed                            | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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         |
| <b>Atelectasis</b>                                     |                 |                 |               |
| subjects affected / exposed                            | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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>Bronchial obstruction</b>                           |                 |                 |               |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed                     | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Chronic obstructive pulmonary disease           |                 |                 |               |
| subjects affected / exposed                     | 4 / 154 (2.60%) | 1 / 150 (0.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 2           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Epistaxis                                       |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 2 / 150 (1.33%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Haemoptysis                                     |                 |                 |               |
| subjects affected / exposed                     | 2 / 154 (1.30%) | 0 / 150 (0.00%) | 0 / 1 (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         |
| Painful respiration                             |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Pleural effusion                                |                 |                 |               |
| subjects affected / exposed                     | 6 / 154 (3.90%) | 3 / 150 (2.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 3           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Pneumonitis                                     |                 |                 |               |
| subjects affected / exposed                     | 6 / 154 (3.90%) | 1 / 150 (0.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 6 / 6           | 1 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Pneumothorax                                    |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 1 / 150 (0.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Pulmonary alveolar haemorrhage                  |                 |                 |               |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed                     | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1           | 0 / 0         |
| <b>Pulmonary embolism</b>                       |                 |                 |               |
| subjects affected / exposed                     | 2 / 154 (1.30%) | 2 / 150 (1.33%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 2           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0         |
| <b>Pulmonary oedema</b>                         |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 2 / 150 (1.33%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| <b>Respiratory failure</b>                      |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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         |
| <b>Acute respiratory distress syndrome</b>      |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| <b>Immune-mediated lung disease</b>             |                 |                 |               |
| subjects affected / exposed                     | 2 / 154 (1.30%) | 0 / 150 (0.00%) | 0 / 1 (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         |
| <b>Laryngeal oedema</b>                         |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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>Psychiatric disorders</b>                    |                 |                 |               |
| <b>Insomnia</b>                                 |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| <b>Restlessness</b>                             |                 |                 |               |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed                     | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Confusional state                               |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Investigations                                  |                 |                 |               |
| Alanine aminotransferase increased              |                 |                 |               |
| subjects affected / exposed                     | 2 / 154 (1.30%) | 0 / 150 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Aspartate aminotransferase increased            |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Bilirubin conjugated increased                  |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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         |
| Platelet count decreased                        |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 1 (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         |
| Transaminases increased                         |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Blood corticotrophin decreased                  |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Blood creatinine increased                      |                 |                 |               |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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         |
| Cortisol decreased                              |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Injury, poisoning and procedural complications  |                 |                 |               |
| Infusion related reaction                       |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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         |
| Pulmonary radiation injury                      |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Radiation oesophagitis                          |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Rib fracture                                    |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Toxicity to various agents                      |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Anastomotic complication                        |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Cardiac disorders                               |                 |                 |               |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| Angina pectoris                                 |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Atrial fibrillation                             |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 2 / 150 (1.33%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Bradycardia                                     |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Cardiac arrest                                  |                 |                 |               |
| subjects affected / exposed                     | 2 / 154 (1.30%) | 1 / 150 (0.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 1           | 0 / 0         |
| Cardiac failure                                 |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 2 / 150 (1.33%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0         |
| Cardio-respiratory arrest                       |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0         |
| Coronary artery disease                         |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 1 / 150 (0.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Ischaemic cardiomyopathy                        |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Pericardial effusion                            |                 |                 |               |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed                     | 1 / 154 (0.65%) | 1 / 150 (0.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| <b>Pericarditis</b>                             |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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>Right ventricular failure</b>                |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| <b>Supraventricular tachycardia</b>             |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 1 / 150 (0.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| <b>Acute myocardial infarction</b>              |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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>Nervous system disorders</b>                 |                 |                 |               |
| <b>Cerebral infarction</b>                      |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| <b>Cerebrovascular accident</b>                 |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 1 / 150 (0.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| <b>Haemorrhagic stroke</b>                      |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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         |
| <b>Ischaemic stroke</b>                         |                 |                 |               |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed                     | 1 / 154 (0.65%) | 1 / 150 (0.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| <b>Transient ischaemic attack</b>               |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| <b>Brain injury</b>                             |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| <b>Brown-Sequard syndrome</b>                   |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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>Cerebral haemorrhage</b>                     |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| <b>Encephalopathy</b>                           |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| <b>Blood and lymphatic system disorders</b>     |                 |                 |               |
| <b>Anaemia</b>                                  |                 |                 |               |
| subjects affected / exposed                     | 2 / 154 (1.30%) | 5 / 150 (3.33%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 5 / 6           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| <b>Febrile neutropenia</b>                      |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 3 / 150 (2.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 3 / 3           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| <b>Leukocytosis</b>                             |                 |                 |               |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed                     | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 1 (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         |
| <b>Pancytopenia</b>                             |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 3 / 150 (2.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 3 / 3           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| <b>Thrombocytopenia</b>                         |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 3 / 150 (2.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 3 / 3           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| <b>Thrombotic microangiopathy</b>               |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0         |
| <b>Ear and labyrinth disorders</b>              |                 |                 |               |
| <b>Vertigo</b>                                  |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| <b>Gastrointestinal disorders</b>               |                 |                 |               |
| <b>Abdominal pain</b>                           |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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>Colitis</b>                                  |                 |                 |               |
| subjects affected / exposed                     | 2 / 154 (1.30%) | 0 / 150 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| <b>Constipation</b>                             |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| <b>Diarrhoea</b>                                |                 |                 |               |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed                     | 3 / 154 (1.95%) | 1 / 150 (0.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 4 / 4           | 1 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| <b>Enterocolitis</b>                            |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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>Faecaloma</b>                                |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| <b>Gastric ulcer</b>                            |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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>Gastritis erosive</b>                        |                 |                 |               |
| subjects affected / exposed                     | 2 / 154 (1.30%) | 0 / 150 (0.00%) | 0 / 1 (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>Nausea</b>                                   |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 2 / 150 (1.33%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| <b>Pancreatitis</b>                             |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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>Small intestinal obstruction</b>             |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| <b>Stomatitis</b>                               |                 |                 |               |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed                     | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 1 (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         |
| Vomiting  |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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         |
| Gastritis                                       |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Intestinal obstruction                          |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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         |
| Oesophagitis                                    |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Oral lichen planus                              |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Hepatobiliary disorders                         |                 |                 |               |
| Acute hepatic failure                           |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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         |
| Autoimmune hepatitis                            |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Skin and subcutaneous tissue disorders          |                 |                 |               |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| Lichenoid keratosis                             |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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         |
| Rash  |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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         |
| Lichen planus                                   |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Rash maculo-papular                             |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 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                     | 0 / 154 (0.00%) | 3 / 150 (2.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 3           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Hypertensive nephropathy                        |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Tubulointerstitial nephritis                    |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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         |
| Endocrine disorders                             |                 |                 |               |
| Hyperthyroidism                                 |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| Hypophysitis                                    |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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 / 154 (0.65%) | 2 / 150 (1.33%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 2           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Back pain                                       |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 3 / 150 (2.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Osteolysis                                      |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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 pain                                     |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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         |
| Haematoma muscle                                |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Muscular weakness                               |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Infections and infestations                     |                 |                 |               |
| Appendicitis                                    |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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         |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| Bronchitis  |                 |                 |               |
| subjects affected / exposed                                   | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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         |
| Cellulitis  |                 |                 |               |
| subjects affected / exposed                                   | 1 / 154 (0.65%) | 1 / 150 (0.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all               | 0 / 1           | 1 / 1           | 0 / 0         |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0         |
| Clostridium difficile colitis                                 |                 |                 |               |
| subjects affected / exposed                                   | 1 / 154 (0.65%) | 2 / 150 (1.33%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all               | 0 / 1           | 0 / 2           | 0 / 0         |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0         |
| Gastroenteritis viral   |                 |                 |               |
| subjects affected / exposed                                   | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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         |
| Infectious pleural effusion                                   |                 |                 |               |
| subjects affected / exposed                                   | 2 / 154 (1.30%) | 0 / 150 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all               | 0 / 3           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all                    | 0 / 1           | 0 / 0           | 0 / 0         |
| Infective exacerbation of chronic obstructive airways disease |                 |                 |               |
| subjects affected / exposed                                   | 2 / 154 (1.30%) | 1 / 150 (0.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all               | 0 / 2           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0         |
| Lower respiratory tract infection                             |                 |                 |               |
| subjects affected / exposed                                   | 5 / 154 (3.25%) | 3 / 150 (2.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all               | 2 / 5           | 0 / 3           | 0 / 0         |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0         |
| Neutropenic sepsis  |                 |                 |               |
| subjects affected / exposed                                   | 1 / 154 (0.65%) | 1 / 150 (0.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all               | 0 / 1           | 1 / 1           | 0 / 0         |
| deaths causally related to treatment / all                    | 0 / 1           | 0 / 0           | 0 / 0         |
| Oral candidiasis  |                 |                 |               |

|   |                 |                  |               |
|---|-----------------|------------------|---------------|
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%)  | 0 / 1 (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         |
| Peritonsillar abscess                           |                 |                  |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 1 / 150 (0.67%)  | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0         |
| Pneumonia                                       |                 |                  |               |
| subjects affected / exposed                     | 6 / 154 (3.90%) | 13 / 150 (8.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 7           | 5 / 13           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0            | 0 / 0         |
| Pulmonary sepsis                                |                 |                  |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 2 / 150 (1.33%)  | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2            | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1            | 0 / 0         |
| Respiratory tract infection                     |                 |                  |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 2 / 150 (1.33%)  | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2            | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0         |
| Sepsis  |                 |                  |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 1 / 150 (0.67%)  | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0         |
| Septic shock                                    |                 |                  |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 1 / 150 (0.67%)  | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0         |
| Skin infection                                  |                 |                  |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 1 / 150 (0.67%)  | 0 / 1 (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         |
| Splenic abscess                                 |                 |                  |               |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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>Urinary tract infection</b>                  |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 2 / 150 (1.33%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 2           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| <b>Urosepsis</b>                                |                 |                 |               |
| subjects affected / exposed                     | 2 / 154 (1.30%) | 0 / 150 (0.00%) | 0 / 1 (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         |
| <b>Bursitis infective</b>                       |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 0 / 150 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| <b>Encephalomyelitis</b>                        |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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>Lymph gland infection</b>                    |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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>Meningitis viral</b>                         |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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>Metabolism and nutrition disorders</b>       |                 |                 |               |
| <b>Decreased appetite</b>                       |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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>Dehydration</b>                              |                 |                 |               |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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         |
| Diabetes mellitus                               |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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         |
| Diabetic ketoacidosis                           |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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         |
| Hypercalcaemia                                  |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 3 / 150 (2.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Hypocalcaemia                                   |                 |                 |               |
| subjects affected / exposed                     | 0 / 154 (0.00%) | 1 / 150 (0.67%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Hyperglycaemia                                  |                 |                 |               |
| subjects affected / exposed                     | 3 / 154 (1.95%) | 0 / 150 (0.00%) | 0 / 1 (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         |
| Hyponatraemia                                   |                 |                 |               |
| subjects affected / exposed                     | 4 / 154 (2.60%) | 0 / 150 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Hypovolaemia                                    |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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         |
| Fluid overload                                  |                 |                 |               |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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>Hypokalaemia</b>                             |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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         |
| <b>Type 2 diabetes mellitus</b>                 |                 |                 |               |
| subjects affected / exposed                     | 1 / 154 (0.65%) | 0 / 150 (0.00%) | 0 / 1 (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>Serious adverse events</b>  | Pembrolizumab<br>Second Course | SOC Chemotherapy<br>Switched Over to<br>Pembrolizumab First<br>Course |  |
|--|--------------------------------|---|--|
| <b>Total subjects affected by serious adverse events</b>                   |                                |   |  |
| subjects affected / exposed  | 2 / 12 (16.67%)                | 27 / 83 (32.53%)  |  |
| number of deaths (all causes)  | 4                              | 62  |  |
| number of deaths resulting from adverse events                             | 0                              | 0   |  |
| <b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b> |                                |   |  |
| <b>Bladder neoplasm</b>  |                                |   |  |
| subjects affected / exposed  | 0 / 12 (0.00%)                 | 0 / 83 (0.00%)  |  |
| occurrences causally related to treatment / all                            | 0 / 0                          | 0 / 0   |  |
| deaths causally related to treatment / all                                 | 0 / 0                          | 0 / 0   |  |
| <b>Cancer pain</b>   |                                |   |  |
| subjects affected / exposed  | 0 / 12 (0.00%)                 | 0 / 83 (0.00%)  |  |
| occurrences causally related to treatment / all                            | 0 / 0                          | 0 / 0   |  |
| deaths causally related to treatment / all                                 | 0 / 0                          | 0 / 0   |  |
| <b>Infected neoplasm</b>   |                                |   |  |
| subjects affected / exposed  | 0 / 12 (0.00%)                 | 0 / 83 (0.00%)  |  |
| occurrences causally related to treatment / all                            | 0 / 0                          | 0 / 0   |  |
| deaths causally related to treatment / all                                 | 0 / 0                          | 0 / 0   |  |
| <b>Malignant neoplasm progression</b>                                      |                                |   |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Appendix cancer                                 |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Bladder cancer                                  |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 1 / 83 (1.20%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Bladder transitional cell carcinoma             |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Colon cancer                                    |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 1 / 83 (1.20%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Colorectal adenocarcinoma                       |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Vascular disorders                              |                |                |  |
| Vasospasm                                       |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Embolism  |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Ischaemia                                       |                |                |  |

|  |                |                |  |
|--|----------------|----------------|--|
| subjects affected / exposed                          | 0 / 12 (0.00%) | 1 / 83 (1.20%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Superior vena cava occlusion                         |                |                |  |
| subjects affected / exposed                          | 1 / 12 (8.33%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| General disorders and administration site conditions |                |                |  |
| Chest pain   |                |                |  |
| subjects affected / exposed                          | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Death  |                |                |  |
| subjects affected / exposed                          | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Face oedema  |                |                |  |
| subjects affected / exposed                          | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Fatigue  |                |                |  |
| subjects affected / exposed                          | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Gait disturbance                                     |                |                |  |
| subjects affected / exposed                          | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| General physical health deterioration                |                |                |  |
| subjects affected / exposed                          | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Multiple organ dysfunction syndrome                  |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Oedema peripheral</b>                        |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Pyrexia</b>                                  |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Sudden death</b>                             |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Immune system disorders</b>                  |                |                |  |
| <b>Anaphylactic shock</b>                       |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Hypersensitivity</b>                         |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Anaphylactic reaction</b>                    |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Reproductive system and breast disorders</b> |                |                |  |
| <b>Ovarian haemorrhage</b>                      |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|   |                |                |  |
|---|----------------|----------------|--|
| Respiratory, thoracic and mediastinal disorders |                |                |  |
| Acute respiratory failure                       |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Atelectasis                                     |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 1 / 83 (1.20%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Bronchial obstruction                           |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Chronic obstructive pulmonary disease           |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 1 / 83 (1.20%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Epistaxis                                       |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Haemoptysis                                     |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 1 / 83 (1.20%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Painful respiration                             |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pleural effusion                                |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|   |                |                |  |
|---|----------------|----------------|--|
| Pneumonitis                                     |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pneumothorax                                    |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pulmonary alveolar haemorrhage                  |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pulmonary embolism                              |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pulmonary oedema                                |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Respiratory failure                             |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Acute respiratory distress syndrome             |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 1 / 83 (1.20%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Immune-mediated lung disease                    |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Laryngeal oedema                                |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Psychiatric disorders</b>                    |                |                |  |
| <b>Insomnia</b>                                 |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Restlessness</b>                             |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Confusional state</b>                        |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 1 / 83 (1.20%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Investigations</b>                           |                |                |  |
| <b>Alanine aminotransferase increased</b>       |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Aspartate aminotransferase increased</b>     |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Bilirubin conjugated increased</b>           |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Platelet count decreased</b>                 |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|   |                |                |  |
|---|----------------|----------------|--|
| Transaminases increased                         |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 1 / 83 (1.20%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Blood corticotrophin decreased                  |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 1 / 83 (1.20%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Blood creatinine increased                      |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cortisol decreased                              |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 1 / 83 (1.20%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Injury, poisoning and procedural complications  |                |                |  |
| Infusion related reaction                       |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pulmonary radiation injury                      |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Radiation oesophagitis                          |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Rib fracture                                    |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|   |                |                |  |
|---|----------------|----------------|--|
| Toxicity to various agents                      |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Anastomotic complication                        |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cardiac disorders                               |                |                |  |
| Angina pectoris                                 |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Atrial fibrillation                             |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 1 / 83 (1.20%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Bradycardia                                     |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cardiac arrest                                  |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cardiac failure                                 |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cardio-respiratory arrest                       |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Coronary artery disease                         |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Ischaemic cardiomyopathy                        |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pericardial effusion                            |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pericarditis                                    |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Right ventricular failure                       |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Supraventricular tachycardia                    |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Acute myocardial infarction                     |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Nervous system disorders                        |                |                |  |
| Cerebral infarction                             |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cerebrovascular accident                        |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 12 (0.00%) | 1 / 83 (1.20%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Haemorrhagic stroke</b>                      |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Ischaemic stroke</b>                         |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Transient ischaemic attack</b>               |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 1 / 83 (1.20%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Brain injury</b>                             |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 1 / 83 (1.20%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Brown-Sequard syndrome</b>                   |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Cerebral haemorrhage</b>                     |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Encephalopathy</b>                           |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 1 / 83 (1.20%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Blood and lymphatic system disorders</b>     |                |                |  |
| Anaemia   |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Febrile neutropenia                             |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Leukocytosis                                    |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pancytopenia                                    |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Thrombocytopenia                                |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Thrombotic microangiopathy                      |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Ear and labyrinth disorders                     |                |                |  |
| Vertigo   |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 1 / 83 (1.20%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastrointestinal disorders                      |                |                |  |
| Abdominal pain                                  |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Colitis   |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Constipation</b>                             |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Diarrhoea</b>                                |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 3 / 83 (3.61%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 3 / 4          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Enterocolitis</b>                            |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Faecaloma</b>                                |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Gastric ulcer</b>                            |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Gastritis erosive</b>                        |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Nausea</b>                                   |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Pancreatitis</b>                             |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Small intestinal obstruction                    |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Stomatitis                                      |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Vomiting  |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastritis                                       |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 1 / 83 (1.20%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Intestinal obstruction                          |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Oesophagitis                                    |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 1 / 83 (1.20%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Oral lichen planus                              |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 1 / 83 (1.20%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Hepatobiliary disorders                         |                |                |  |
| Acute hepatic failure                           |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Autoimmune hepatitis                            |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Skin and subcutaneous tissue disorders          |                |                |  |
| Lichenoid keratosis                             |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Rash  |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Lichen planus                                   |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 1 / 83 (1.20%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Rash maculo-papular                             |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 1 / 83 (1.20%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Renal and urinary disorders                     |                |                |  |
| Acute kidney injury                             |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Hypertensive nephropathy                        |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Tubulointerstitial nephritis                    |                |                |  |

|  |                |                |  |
|--|----------------|----------------|--|
| subjects affected / exposed                            | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          |  |
| <b>Endocrine disorders</b>                             |                |                |  |
| <b>Hyperthyroidism</b>                                 |                |                |  |
| subjects affected / exposed                            | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          |  |
| <b>Hypophysitis</b>                                    |                |                |  |
| subjects affected / exposed                            | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          |  |
| <b>Musculoskeletal and connective tissue disorders</b> |                |                |  |
| <b>Arthralgia</b>                                      |                |                |  |
| subjects affected / exposed                            | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          |  |
| <b>Back pain</b>                                       |                |                |  |
| subjects affected / exposed                            | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          |  |
| <b>Osteolysis</b>                                      |                |                |  |
| subjects affected / exposed                            | 0 / 12 (0.00%) | 1 / 83 (1.20%) |  |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          |  |
| <b>Spinal pain</b>                                     |                |                |  |
| subjects affected / exposed                            | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          |  |
| <b>Haematoma muscle</b>                                |                |                |  |
| subjects affected / exposed                            | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          |  |

|  |                |                |  |
|--|----------------|----------------|--|
| Muscular weakness  |                |                |  |
| subjects affected / exposed  | 0 / 12 (0.00%) | 1 / 83 (1.20%) |  |
| occurrences causally related to treatment / all                      | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all                           | 0 / 0          | 0 / 0          |  |
| <b>Infections and infestations</b>                                   |                |                |  |
| <b>Appendicitis</b>  |                |                |  |
| subjects affected / exposed  | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all                      | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all                           | 0 / 0          | 0 / 0          |  |
| <b>Bronchitis</b>  |                |                |  |
| subjects affected / exposed  | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all                      | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all                           | 0 / 0          | 0 / 0          |  |
| <b>Cellulitis</b>  |                |                |  |
| subjects affected / exposed  | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all                      | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all                           | 0 / 0          | 0 / 0          |  |
| <b>Clostridium difficile colitis</b>                                 |                |                |  |
| subjects affected / exposed  | 0 / 12 (0.00%) | 2 / 83 (2.41%) |  |
| occurrences causally related to treatment / all                      | 0 / 0          | 0 / 2          |  |
| deaths causally related to treatment / all                           | 0 / 0          | 0 / 0          |  |
| <b>Gastroenteritis viral</b>   |                |                |  |
| subjects affected / exposed  | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all                      | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all                           | 0 / 0          | 0 / 0          |  |
| <b>Infectious pleural effusion</b>                                   |                |                |  |
| subjects affected / exposed  | 0 / 12 (0.00%) | 1 / 83 (1.20%) |  |
| occurrences causally related to treatment / all                      | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all                           | 0 / 0          | 0 / 0          |  |
| <b>Infective exacerbation of chronic obstructive airways disease</b> |                |                |  |
| subjects affected / exposed  | 0 / 12 (0.00%) | 1 / 83 (1.20%) |  |
| occurrences causally related to treatment / all                      | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all                           | 0 / 0          | 0 / 0          |  |

|   |                |                |  |
|---|----------------|----------------|--|
| Lower respiratory tract infection               |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 1 / 83 (1.20%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| Neutropenic sepsis                              |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Oral candidiasis                                |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Peritonsillar abscess                           |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pneumonia                                       |                |                |  |
| subjects affected / exposed                     | 1 / 12 (8.33%) | 2 / 83 (2.41%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 1 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| Pulmonary sepsis                                |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Respiratory tract infection                     |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Sepsis  |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 1 / 83 (1.20%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Septic shock                                    |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Skin infection</b>                           |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Splenic abscess</b>                          |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Urinary tract infection</b>                  |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Urosepsis</b>                                |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Bursitis infective</b>                       |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 1 / 83 (1.20%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Encephalomyelitis</b>                        |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Lymph gland infection</b>                    |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Meningitis viral</b>                         |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Metabolism and nutrition disorders</b>       |                |                |  |
| <b>Decreased appetite</b>                       |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Dehydration</b>                              |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Diabetes mellitus</b>                        |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Diabetic ketoacidosis</b>                    |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Hypercalcaemia</b>                           |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 1 / 83 (1.20%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Hypocalcaemia</b>                            |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Hyperglycaemia</b>                           |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Hyponatraemia</b>                            |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Hypovolaemia</b>                             |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Fluid overload</b>                           |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Hypokalaemia</b>                             |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Type 2 diabetes mellitus</b>                 |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 83 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

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

| <b>Non-serious adverse events</b>  | Pembrolizumab First Course | SOC Chemotherapy First Course | SOC Chemotherapy Switched over to Second Course Pembrolizumab |
|--|----------------------------|-------------------------------|---|
| Total subjects affected by non-serious adverse events                      |                            |                               |   |
| subjects affected / exposed  | 140 / 154 (90.91%)         | 142 / 150 (94.67%)            | 0 / 1 (0.00%)   |
| <b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b> |                            |                               |   |
| <b>Tumour pain</b>   |                            |                               |   |
| subjects affected / exposed  | 1 / 154 (0.65%)            | 0 / 150 (0.00%)               | 0 / 1 (0.00%)   |
| occurrences (all)  | 1                          | 0                             | 0   |
| <b>Vascular disorders</b>  |                            |                               |   |
| <b>Hypertension</b>  |                            |                               |   |
| subjects affected / exposed  | 11 / 154 (7.14%)           | 4 / 150 (2.67%)               | 0 / 1 (0.00%)   |
| occurrences (all)  | 13                         | 4                             | 0   |

|  |                         |                         |                    |
|--|-------------------------|-------------------------|--------------------|
| Hypotension<br>subjects affected / exposed<br>occurrences (all)            | 4 / 154 (2.60%)<br>5    | 4 / 150 (2.67%)<br>4    | 0 / 1 (0.00%)<br>0 |
| General disorders and administration site conditions                       |                         |                         |                    |
| Asthenia<br>subjects affected / exposed<br>occurrences (all)               | 12 / 154 (7.79%)<br>17  | 17 / 150 (11.33%)<br>30 | 0 / 1 (0.00%)<br>0 |
| Chest pain<br>subjects affected / exposed<br>occurrences (all)             | 16 / 154 (10.39%)<br>17 | 16 / 150 (10.67%)<br>16 | 0 / 1 (0.00%)<br>0 |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)                | 37 / 154 (24.03%)<br>45 | 53 / 150 (35.33%)<br>93 | 0 / 1 (0.00%)<br>0 |
| Malaise<br>subjects affected / exposed<br>occurrences (all)                | 6 / 154 (3.90%)<br>6    | 12 / 150 (8.00%)<br>13  | 0 / 1 (0.00%)<br>0 |
| Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)      | 19 / 154 (12.34%)<br>20 | 15 / 150 (10.00%)<br>19 | 0 / 1 (0.00%)<br>0 |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)                | 27 / 154 (17.53%)<br>36 | 14 / 150 (9.33%)<br>16  | 0 / 1 (0.00%)<br>0 |
| Influenza like illness<br>subjects affected / exposed<br>occurrences (all) | 2 / 154 (1.30%)<br>2    | 2 / 150 (1.33%)<br>7    | 0 / 1 (0.00%)<br>0 |
| Respiratory, thoracic and mediastinal disorders                            |                         |                         |                    |
| Cough<br>subjects affected / exposed<br>occurrences (all)                  | 29 / 154 (18.83%)<br>44 | 21 / 150 (14.00%)<br>24 | 0 / 1 (0.00%)<br>0 |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)               | 41 / 154 (26.62%)<br>50 | 24 / 150 (16.00%)<br>29 | 0 / 1 (0.00%)<br>0 |
| Haemoptysis<br>subjects affected / exposed<br>occurrences (all)            | 11 / 154 (7.14%)<br>11  | 5 / 150 (3.33%)<br>5    | 0 / 1 (0.00%)<br>0 |
| Hiccups  |                         |                         |                    |

|   |                         |                         |                    |
|---|-------------------------|-------------------------|--------------------|
| subjects affected / exposed<br>occurrences (all)  | 2 / 154 (1.30%)<br>2    | 10 / 150 (6.67%)<br>12  | 0 / 1 (0.00%)<br>0 |
| Nasal congestion<br>subjects affected / exposed<br>occurrences (all)  | 1 / 154 (0.65%)<br>1    | 2 / 150 (1.33%)<br>2    | 0 / 1 (0.00%)<br>0 |
| Psychiatric disorders<br>Insomnia<br>subjects affected / exposed<br>occurrences (all)                         | 16 / 154 (10.39%)<br>18 | 11 / 150 (7.33%)<br>11  | 0 / 1 (0.00%)<br>0 |
| Investigations<br>Aspartate aminotransferase<br>increased<br>subjects affected / exposed<br>occurrences (all) | 15 / 154 (9.74%)<br>19  | 7 / 150 (4.67%)<br>9    | 0 / 1 (0.00%)<br>0 |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)                        | 17 / 154 (11.04%)<br>20 | 11 / 150 (7.33%)<br>15  | 0 / 1 (0.00%)<br>0 |
| Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all)                      | 10 / 154 (6.49%)<br>14  | 4 / 150 (2.67%)<br>4    | 0 / 1 (0.00%)<br>0 |
| Blood creatinine increased<br>subjects affected / exposed<br>occurrences (all)                                | 12 / 154 (7.79%)<br>15  | 21 / 150 (14.00%)<br>26 | 0 / 1 (0.00%)<br>0 |
| Neutrophil count decreased<br>subjects affected / exposed<br>occurrences (all)                                | 1 / 154 (0.65%)<br>3    | 21 / 150 (14.00%)<br>37 | 0 / 1 (0.00%)<br>0 |
| Platelet count decreased<br>subjects affected / exposed<br>occurrences (all)                                  | 1 / 154 (0.65%)<br>1    | 19 / 150 (12.67%)<br>28 | 0 / 1 (0.00%)<br>0 |
| White blood cell count decreased<br>subjects affected / exposed<br>occurrences (all)                          | 1 / 154 (0.65%)<br>3    | 17 / 150 (11.33%)<br>25 | 0 / 1 (0.00%)<br>0 |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)  | 14 / 154 (9.09%)<br>15  | 11 / 150 (7.33%)<br>12  | 0 / 1 (0.00%)<br>0 |
| Injury, poisoning and procedural<br>complications   |                         |                         |                    |

|                                      |                   |                   |               |
|--------------------------------------|-------------------|-------------------|---------------|
| Eye injury                           |                   |                   |               |
| subjects affected / exposed          | 0 / 154 (0.00%)   | 0 / 150 (0.00%)   | 0 / 1 (0.00%) |
| occurrences (all)                    | 0                 | 0                 | 0             |
| Fall                                 |                   |                   |               |
| subjects affected / exposed          | 9 / 154 (5.84%)   | 4 / 150 (2.67%)   | 0 / 1 (0.00%) |
| occurrences (all)                    | 9                 | 4                 | 0             |
| Ligament sprain                      |                   |                   |               |
| subjects affected / exposed          | 2 / 154 (1.30%)   | 1 / 150 (0.67%)   | 0 / 1 (0.00%) |
| occurrences (all)                    | 2                 | 1                 | 0             |
| Cardiac disorders                    |                   |                   |               |
| Bradycardia                          |                   |                   |               |
| subjects affected / exposed          | 1 / 154 (0.65%)   | 1 / 150 (0.67%)   | 0 / 1 (0.00%) |
| occurrences (all)                    | 1                 | 1                 | 0             |
| Nervous system disorders             |                   |                   |               |
| Dizziness                            |                   |                   |               |
| subjects affected / exposed          | 20 / 154 (12.99%) | 12 / 150 (8.00%)  | 0 / 1 (0.00%) |
| occurrences (all)                    | 25                | 16                | 0             |
| Dysgeusia                            |                   |                   |               |
| subjects affected / exposed          | 2 / 154 (1.30%)   | 13 / 150 (8.67%)  | 0 / 1 (0.00%) |
| occurrences (all)                    | 2                 | 13                | 0             |
| Headache                             |                   |                   |               |
| subjects affected / exposed          | 11 / 154 (7.14%)  | 7 / 150 (4.67%)   | 0 / 1 (0.00%) |
| occurrences (all)                    | 17                | 8                 | 0             |
| Neuropathy peripheral                |                   |                   |               |
| subjects affected / exposed          | 2 / 154 (1.30%)   | 10 / 150 (6.67%)  | 0 / 1 (0.00%) |
| occurrences (all)                    | 2                 | 10                | 0             |
| Tremor                               |                   |                   |               |
| subjects affected / exposed          | 1 / 154 (0.65%)   | 2 / 150 (1.33%)   | 0 / 1 (0.00%) |
| occurrences (all)                    | 1                 | 2                 | 0             |
| Blood and lymphatic system disorders |                   |                   |               |
| Leukopenia                           |                   |                   |               |
| subjects affected / exposed          | 1 / 154 (0.65%)   | 10 / 150 (6.67%)  | 0 / 1 (0.00%) |
| occurrences (all)                    | 1                 | 17                | 0             |
| Neutropenia                          |                   |                   |               |
| subjects affected / exposed          | 2 / 154 (1.30%)   | 35 / 150 (23.33%) | 0 / 1 (0.00%) |
| occurrences (all)                    | 4                 | 67                | 0             |
| Anaemia                              |                   |                   |               |

|  |                         |                          |                    |
|--|-------------------------|--------------------------|--------------------|
| subjects affected / exposed<br>occurrences (all)   | 24 / 154 (15.58%)<br>28 | 77 / 150 (51.33%)<br>98  | 0 / 1 (0.00%)<br>0 |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)                             | 2 / 154 (1.30%)<br>2    | 18 / 150 (12.00%)<br>32  | 0 / 1 (0.00%)<br>0 |
| Eye disorders<br>Conjunctivitis allergic<br>subjects affected / exposed<br>occurrences (all)     | 1 / 154 (0.65%)<br>1    | 0 / 150 (0.00%)<br>0     | 0 / 1 (0.00%)<br>0 |
| Gastrointestinal disorders<br>Abdominal pain<br>subjects affected / exposed<br>occurrences (all) | 14 / 154 (9.09%)<br>17  | 10 / 150 (6.67%)<br>10   | 0 / 1 (0.00%)<br>0 |
| Constipation<br>subjects affected / exposed<br>occurrences (all)                                 | 35 / 154 (22.73%)<br>43 | 33 / 150 (22.00%)<br>54  | 0 / 1 (0.00%)<br>0 |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                                    | 41 / 154 (26.62%)<br>65 | 33 / 150 (22.00%)<br>43  | 0 / 1 (0.00%)<br>0 |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)                                    | 6 / 154 (3.90%)<br>7    | 9 / 150 (6.00%)<br>14    | 0 / 1 (0.00%)<br>0 |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                                       | 33 / 154 (21.43%)<br>44 | 68 / 150 (45.33%)<br>129 | 0 / 1 (0.00%)<br>0 |
| Stomatitis<br>subjects affected / exposed<br>occurrences (all)                                   | 8 / 154 (5.19%)<br>8    | 17 / 150 (11.33%)<br>23  | 0 / 1 (0.00%)<br>0 |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                                     | 16 / 154 (10.39%)<br>20 | 36 / 150 (24.00%)<br>65  | 0 / 1 (0.00%)<br>0 |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)                         | 7 / 154 (4.55%)<br>9    | 7 / 150 (4.67%)<br>13    | 0 / 1 (0.00%)<br>0 |
| Dysphagia  |                         |                          |                    |

|   |                         |                         |                    |
|---|-------------------------|-------------------------|--------------------|
| subjects affected / exposed<br>occurrences (all)                        | 2 / 154 (1.30%)<br>2    | 6 / 150 (4.00%)<br>6    | 0 / 1 (0.00%)<br>0 |
| Oesophagitis<br>subjects affected / exposed<br>occurrences (all)        | 1 / 154 (0.65%)<br>1    | 1 / 150 (0.67%)<br>1    | 0 / 1 (0.00%)<br>0 |
| <b>Skin and subcutaneous tissue disorders</b>                           |                         |                         |                    |
| Alopecia<br>subjects affected / exposed<br>occurrences (all)            | 2 / 154 (1.30%)<br>2    | 15 / 150 (10.00%)<br>15 | 0 / 1 (0.00%)<br>0 |
| Dry skin<br>subjects affected / exposed<br>occurrences (all)            | 17 / 154 (11.04%)<br>18 | 1 / 150 (0.67%)<br>1    | 0 / 1 (0.00%)<br>0 |
| Pruritus<br>subjects affected / exposed<br>occurrences (all)            | 32 / 154 (20.78%)<br>46 | 6 / 150 (4.00%)<br>6    | 0 / 1 (0.00%)<br>0 |
| Rash<br>subjects affected / exposed<br>occurrences (all)                | 28 / 154 (18.18%)<br>43 | 7 / 150 (4.67%)<br>8    | 0 / 1 (0.00%)<br>0 |
| Panniculitis<br>subjects affected / exposed<br>occurrences (all)        | 0 / 154 (0.00%)<br>0    | 0 / 150 (0.00%)<br>0    | 0 / 1 (0.00%)<br>0 |
| Rash maculo-papular<br>subjects affected / exposed<br>occurrences (all) | 7 / 154 (4.55%)<br>8    | 1 / 150 (0.67%)<br>2    | 0 / 1 (0.00%)<br>0 |
| <b>Endocrine disorders</b>  |                         |                         |                    |
| Hyperthyroidism<br>subjects affected / exposed<br>occurrences (all)     | 10 / 154 (6.49%)<br>11  | 2 / 150 (1.33%)<br>3    | 0 / 1 (0.00%)<br>0 |
| Hypothyroidism<br>subjects affected / exposed<br>occurrences (all)      | 16 / 154 (10.39%)<br>16 | 3 / 150 (2.00%)<br>3    | 0 / 1 (0.00%)<br>0 |
| <b>Musculoskeletal and connective tissue disorders</b>                  |                         |                         |                    |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)          | 34 / 154 (22.08%)<br>47 | 17 / 150 (11.33%)<br>21 | 0 / 1 (0.00%)<br>0 |
| Back pain   |                         |                         |                    |

|                                   |                   |                   |               |
|-----------------------------------|-------------------|-------------------|---------------|
| subjects affected / exposed       | 23 / 154 (14.94%) | 18 / 150 (12.00%) | 0 / 1 (0.00%) |
| occurrences (all)                 | 26                | 21                | 0             |
| Muscle spasms                     |                   |                   |               |
| subjects affected / exposed       | 10 / 154 (6.49%)  | 2 / 150 (1.33%)   | 0 / 1 (0.00%) |
| occurrences (all)                 | 10                | 2                 | 0             |
| Pain in extremity                 |                   |                   |               |
| subjects affected / exposed       | 9 / 154 (5.84%)   | 10 / 150 (6.67%)  | 0 / 1 (0.00%) |
| occurrences (all)                 | 12                | 13                | 0             |
| Myalgia                           |                   |                   |               |
| subjects affected / exposed       | 10 / 154 (6.49%)  | 2 / 150 (1.33%)   | 0 / 1 (0.00%) |
| occurrences (all)                 | 11                | 2                 | 0             |
| Periarthritis                     |                   |                   |               |
| subjects affected / exposed       | 0 / 154 (0.00%)   | 0 / 150 (0.00%)   | 0 / 1 (0.00%) |
| occurrences (all)                 | 0                 | 0                 | 0             |
| Infections and infestations       |                   |                   |               |
| Upper respiratory tract infection |                   |                   |               |
| subjects affected / exposed       | 11 / 154 (7.14%)  | 5 / 150 (3.33%)   | 0 / 1 (0.00%) |
| occurrences (all)                 | 18                | 7                 | 0             |
| Nasopharyngitis                   |                   |                   |               |
| subjects affected / exposed       | 18 / 154 (11.69%) | 2 / 150 (1.33%)   | 0 / 1 (0.00%) |
| occurrences (all)                 | 27                | 2                 | 0             |
| Bronchitis                        |                   |                   |               |
| subjects affected / exposed       | 8 / 154 (5.19%)   | 4 / 150 (2.67%)   | 0 / 1 (0.00%) |
| occurrences (all)                 | 9                 | 5                 | 0             |
| Infected dermal cyst              |                   |                   |               |
| subjects affected / exposed       | 1 / 154 (0.65%)   | 0 / 150 (0.00%)   | 0 / 1 (0.00%) |
| occurrences (all)                 | 1                 | 0                 | 0             |
| Influenza                         |                   |                   |               |
| subjects affected / exposed       | 2 / 154 (1.30%)   | 2 / 150 (1.33%)   | 0 / 1 (0.00%) |
| occurrences (all)                 | 2                 | 3                 | 0             |
| Tooth infection                   |                   |                   |               |
| subjects affected / exposed       | 2 / 154 (1.30%)   | 2 / 150 (1.33%)   | 0 / 1 (0.00%) |
| occurrences (all)                 | 2                 | 2                 | 0             |
| Sinusitis                         |                   |                   |               |
| subjects affected / exposed       | 2 / 154 (1.30%)   | 2 / 150 (1.33%)   | 0 / 1 (0.00%) |
| occurrences (all)                 | 2                 | 2                 | 0             |

|  |                         |                         |                    |
|--|-------------------------|-------------------------|--------------------|
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)                                  | 9 / 154 (5.84%)<br>11   | 8 / 150 (5.33%)<br>11   | 0 / 1 (0.00%)<br>0 |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all) | 33 / 154 (21.43%)<br>36 | 49 / 150 (32.67%)<br>71 | 0 / 1 (0.00%)<br>0 |
| Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all)   | 10 / 154 (6.49%)<br>17  | 9 / 150 (6.00%)<br>10   | 0 / 1 (0.00%)<br>0 |
| Hypomagnesaemia<br>subjects affected / exposed<br>occurrences (all)  | 4 / 154 (2.60%)<br>7    | 13 / 150 (8.67%)<br>18  | 0 / 1 (0.00%)<br>0 |
| Hyponatraemia<br>subjects affected / exposed<br>occurrences (all)  | 11 / 154 (7.14%)<br>17  | 12 / 150 (8.00%)<br>13  | 0 / 1 (0.00%)<br>0 |
| Hyperkalaemia<br>subjects affected / exposed<br>occurrences (all)  | 8 / 154 (5.19%)<br>9    | 6 / 150 (4.00%)<br>7    | 0 / 1 (0.00%)<br>0 |
| Hypoalbuminaemia<br>subjects affected / exposed<br>occurrences (all)   | 8 / 154 (5.19%)<br>8    | 7 / 150 (4.67%)<br>7    | 0 / 1 (0.00%)<br>0 |

| <b>Non-serious adverse events</b>   | Pembrolizumab<br>Second Course | SOC Chemotherapy<br>Switched Over to<br>Pembrolizumab First<br>Course |  |
|---|--------------------------------|---|--|
| Total subjects affected by non-serious<br>adverse events<br>subjects affected / exposed   | 10 / 12 (83.33%)               | 72 / 83 (86.75%)  |  |
| Neoplasms benign, malignant and<br>unspecified (incl cysts and polyps)<br>Tumour pain<br>subjects affected / exposed<br>occurrences (all) | 1 / 12 (8.33%)<br>1            | 0 / 83 (0.00%)<br>0   |  |
| Vascular disorders<br>Hypertension<br>subjects affected / exposed<br>occurrences (all)  | 0 / 12 (0.00%)<br>0            | 0 / 83 (0.00%)<br>0   |  |
| Hypotension   |                                |   |  |

|   |                     |                        |  |
|---|---------------------|------------------------|--|
| subjects affected / exposed<br>occurrences (all)        | 1 / 12 (8.33%)<br>1 | 2 / 83 (2.41%)<br>2    |  |
| General disorders and administration<br>site conditions |                     |                        |  |
| Asthenia  |                     |                        |  |
| subjects affected / exposed<br>occurrences (all)        | 0 / 12 (0.00%)<br>0 | 7 / 83 (8.43%)<br>7    |  |
| Chest pain  |                     |                        |  |
| subjects affected / exposed<br>occurrences (all)        | 0 / 12 (0.00%)<br>0 | 5 / 83 (6.02%)<br>6    |  |
| Fatigue   |                     |                        |  |
| subjects affected / exposed<br>occurrences (all)        | 1 / 12 (8.33%)<br>1 | 18 / 83 (21.69%)<br>19 |  |
| Malaise   |                     |                        |  |
| subjects affected / exposed<br>occurrences (all)        | 0 / 12 (0.00%)<br>0 | 1 / 83 (1.20%)<br>2    |  |
| Oedema peripheral                                       |                     |                        |  |
| subjects affected / exposed<br>occurrences (all)        | 0 / 12 (0.00%)<br>0 | 3 / 83 (3.61%)<br>4    |  |
| Pyrexia   |                     |                        |  |
| subjects affected / exposed<br>occurrences (all)        | 0 / 12 (0.00%)<br>0 | 8 / 83 (9.64%)<br>8    |  |
| Influenza like illness                                  |                     |                        |  |
| subjects affected / exposed<br>occurrences (all)        | 1 / 12 (8.33%)<br>1 | 3 / 83 (3.61%)<br>4    |  |
| Respiratory, thoracic and mediastinal<br>disorders      |                     |                        |  |
| Cough   |                     |                        |  |
| subjects affected / exposed<br>occurrences (all)        | 1 / 12 (8.33%)<br>1 | 16 / 83 (19.28%)<br>17 |  |
| Dyspnoea  |                     |                        |  |
| subjects affected / exposed<br>occurrences (all)        | 0 / 12 (0.00%)<br>0 | 9 / 83 (10.84%)<br>10  |  |
| Haemoptysis   |                     |                        |  |
| subjects affected / exposed<br>occurrences (all)        | 1 / 12 (8.33%)<br>1 | 7 / 83 (8.43%)<br>10   |  |
| Hiccups   |                     |                        |  |

|   |                      |                     |  |
|---|----------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all)  | 0 / 12 (0.00%)<br>0  | 1 / 83 (1.20%)<br>1 |  |
| Nasal congestion<br>subjects affected / exposed<br>occurrences (all)  | 1 / 12 (8.33%)<br>1  | 3 / 83 (3.61%)<br>3 |  |
| Psychiatric disorders<br>Insomnia<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 12 (0.00%)<br>0  | 7 / 83 (8.43%)<br>7 |  |
| Investigations<br>Aspartate aminotransferase<br>increased<br>subjects affected / exposed<br>occurrences (all) | 1 / 12 (8.33%)<br>1  | 4 / 83 (4.82%)<br>4 |  |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)                        | 1 / 12 (8.33%)<br>1  | 4 / 83 (4.82%)<br>4 |  |
| Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all)                      | 1 / 12 (8.33%)<br>1  | 2 / 83 (2.41%)<br>2 |  |
| Blood creatinine increased<br>subjects affected / exposed<br>occurrences (all)                                | 0 / 12 (0.00%)<br>0  | 5 / 83 (6.02%)<br>9 |  |
| Neutrophil count decreased<br>subjects affected / exposed<br>occurrences (all)                                | 0 / 12 (0.00%)<br>0  | 0 / 83 (0.00%)<br>0 |  |
| Platelet count decreased<br>subjects affected / exposed<br>occurrences (all)                                  | 0 / 12 (0.00%)<br>0  | 1 / 83 (1.20%)<br>1 |  |
| White blood cell count decreased<br>subjects affected / exposed<br>occurrences (all)                          | 1 / 12 (8.33%)<br>1  | 1 / 83 (1.20%)<br>1 |  |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)  | 2 / 12 (16.67%)<br>2 | 6 / 83 (7.23%)<br>8 |  |
| Injury, poisoning and procedural<br>complications   |                      |                     |  |

|                                      |                |                |  |
|--------------------------------------|----------------|----------------|--|
| Eye injury                           |                |                |  |
| subjects affected / exposed          | 1 / 12 (8.33%) | 0 / 83 (0.00%) |  |
| occurrences (all)                    | 1              | 0              |  |
| Fall                                 |                |                |  |
| subjects affected / exposed          | 0 / 12 (0.00%) | 3 / 83 (3.61%) |  |
| occurrences (all)                    | 0              | 5              |  |
| Ligament sprain                      |                |                |  |
| subjects affected / exposed          | 1 / 12 (8.33%) | 0 / 83 (0.00%) |  |
| occurrences (all)                    | 1              | 0              |  |
| Cardiac disorders                    |                |                |  |
| Bradycardia                          |                |                |  |
| subjects affected / exposed          | 1 / 12 (8.33%) | 0 / 83 (0.00%) |  |
| occurrences (all)                    | 1              | 0              |  |
| Nervous system disorders             |                |                |  |
| Dizziness                            |                |                |  |
| subjects affected / exposed          | 0 / 12 (0.00%) | 5 / 83 (6.02%) |  |
| occurrences (all)                    | 0              | 7              |  |
| Dysgeusia                            |                |                |  |
| subjects affected / exposed          | 0 / 12 (0.00%) | 1 / 83 (1.20%) |  |
| occurrences (all)                    | 0              | 1              |  |
| Headache                             |                |                |  |
| subjects affected / exposed          | 0 / 12 (0.00%) | 7 / 83 (8.43%) |  |
| occurrences (all)                    | 0              | 7              |  |
| Neuropathy peripheral                |                |                |  |
| subjects affected / exposed          | 0 / 12 (0.00%) | 3 / 83 (3.61%) |  |
| occurrences (all)                    | 0              | 3              |  |
| Tremor                               |                |                |  |
| subjects affected / exposed          | 1 / 12 (8.33%) | 0 / 83 (0.00%) |  |
| occurrences (all)                    | 1              | 0              |  |
| Blood and lymphatic system disorders |                |                |  |
| Leukopenia                           |                |                |  |
| subjects affected / exposed          | 1 / 12 (8.33%) | 0 / 83 (0.00%) |  |
| occurrences (all)                    | 1              | 0              |  |
| Neutropenia                          |                |                |  |
| subjects affected / exposed          | 1 / 12 (8.33%) | 1 / 83 (1.20%) |  |
| occurrences (all)                    | 1              | 1              |  |
| Anaemia                              |                |                |  |

|  |                      |                        |  |
|--|----------------------|------------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 0 / 12 (0.00%)<br>0  | 4 / 83 (4.82%)<br>4    |  |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)                             | 0 / 12 (0.00%)<br>0  | 0 / 83 (0.00%)<br>0    |  |
| Eye disorders<br>Conjunctivitis allergic<br>subjects affected / exposed<br>occurrences (all)     | 1 / 12 (8.33%)<br>1  | 1 / 83 (1.20%)<br>1    |  |
| Gastrointestinal disorders<br>Abdominal pain<br>subjects affected / exposed<br>occurrences (all) | 1 / 12 (8.33%)<br>1  | 7 / 83 (8.43%)<br>7    |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)                                 | 2 / 12 (16.67%)<br>2 | 7 / 83 (8.43%)<br>7    |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                                    | 1 / 12 (8.33%)<br>1  | 18 / 83 (21.69%)<br>22 |  |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)                                    | 1 / 12 (8.33%)<br>2  | 3 / 83 (3.61%)<br>3    |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                                       | 1 / 12 (8.33%)<br>1  | 15 / 83 (18.07%)<br>19 |  |
| Stomatitis<br>subjects affected / exposed<br>occurrences (all)                                   | 0 / 12 (0.00%)<br>0  | 3 / 83 (3.61%)<br>3    |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 12 (0.00%)<br>0  | 8 / 83 (9.64%)<br>9    |  |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 12 (8.33%)<br>1  | 2 / 83 (2.41%)<br>2    |  |
| Dysphagia  |                      |                        |  |

|   |                      |                        |  |
|---|----------------------|------------------------|--|
| subjects affected / exposed<br>occurrences (all)                        | 1 / 12 (8.33%)<br>1  | 3 / 83 (3.61%)<br>3    |  |
| Oesophagitis<br>subjects affected / exposed<br>occurrences (all)        | 1 / 12 (8.33%)<br>1  | 0 / 83 (0.00%)<br>0    |  |
| <b>Skin and subcutaneous tissue disorders</b>                           |                      |                        |  |
| Alopecia<br>subjects affected / exposed<br>occurrences (all)            | 0 / 12 (0.00%)<br>0  | 2 / 83 (2.41%)<br>2    |  |
| Dry skin<br>subjects affected / exposed<br>occurrences (all)            | 1 / 12 (8.33%)<br>1  | 7 / 83 (8.43%)<br>7    |  |
| Pruritus<br>subjects affected / exposed<br>occurrences (all)            | 2 / 12 (16.67%)<br>2 | 13 / 83 (15.66%)<br>13 |  |
| Rash<br>subjects affected / exposed<br>occurrences (all)                | 0 / 12 (0.00%)<br>0  | 8 / 83 (9.64%)<br>13   |  |
| Panniculitis<br>subjects affected / exposed<br>occurrences (all)        | 1 / 12 (8.33%)<br>1  | 0 / 83 (0.00%)<br>0    |  |
| Rash maculo-papular<br>subjects affected / exposed<br>occurrences (all) | 0 / 12 (0.00%)<br>0  | 6 / 83 (7.23%)<br>6    |  |
| <b>Endocrine disorders</b>  |                      |                        |  |
| Hyperthyroidism<br>subjects affected / exposed<br>occurrences (all)     | 0 / 12 (0.00%)<br>0  | 5 / 83 (6.02%)<br>7    |  |
| Hypothyroidism<br>subjects affected / exposed<br>occurrences (all)      | 1 / 12 (8.33%)<br>1  | 8 / 83 (9.64%)<br>8    |  |
| <b>Musculoskeletal and connective tissue disorders</b>                  |                      |                        |  |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)          | 0 / 12 (0.00%)<br>0  | 16 / 83 (19.28%)<br>18 |  |
| Back pain   |                      |                        |  |

|                                   |                 |                 |  |
|-----------------------------------|-----------------|-----------------|--|
| subjects affected / exposed       | 0 / 12 (0.00%)  | 4 / 83 (4.82%)  |  |
| occurrences (all)                 | 0               | 4               |  |
| Muscle spasms                     |                 |                 |  |
| subjects affected / exposed       | 0 / 12 (0.00%)  | 2 / 83 (2.41%)  |  |
| occurrences (all)                 | 0               | 3               |  |
| Pain in extremity                 |                 |                 |  |
| subjects affected / exposed       | 1 / 12 (8.33%)  | 6 / 83 (7.23%)  |  |
| occurrences (all)                 | 1               | 8               |  |
| Myalgia                           |                 |                 |  |
| subjects affected / exposed       | 0 / 12 (0.00%)  | 5 / 83 (6.02%)  |  |
| occurrences (all)                 | 0               | 5               |  |
| Periarthritis                     |                 |                 |  |
| subjects affected / exposed       | 1 / 12 (8.33%)  | 0 / 83 (0.00%)  |  |
| occurrences (all)                 | 1               | 0               |  |
| Infections and infestations       |                 |                 |  |
| Upper respiratory tract infection |                 |                 |  |
| subjects affected / exposed       | 4 / 12 (33.33%) | 9 / 83 (10.84%) |  |
| occurrences (all)                 | 4               | 12              |  |
| Nasopharyngitis                   |                 |                 |  |
| subjects affected / exposed       | 2 / 12 (16.67%) | 9 / 83 (10.84%) |  |
| occurrences (all)                 | 2               | 10              |  |
| Bronchitis                        |                 |                 |  |
| subjects affected / exposed       | 0 / 12 (0.00%)  | 5 / 83 (6.02%)  |  |
| occurrences (all)                 | 0               | 6               |  |
| Infected dermal cyst              |                 |                 |  |
| subjects affected / exposed       | 1 / 12 (8.33%)  | 0 / 83 (0.00%)  |  |
| occurrences (all)                 | 1               | 0               |  |
| Influenza                         |                 |                 |  |
| subjects affected / exposed       | 1 / 12 (8.33%)  | 1 / 83 (1.20%)  |  |
| occurrences (all)                 | 1               | 1               |  |
| Tooth infection                   |                 |                 |  |
| subjects affected / exposed       | 1 / 12 (8.33%)  | 2 / 83 (2.41%)  |  |
| occurrences (all)                 | 1               | 3               |  |
| Sinusitis                         |                 |                 |  |
| subjects affected / exposed       | 1 / 12 (8.33%)  | 2 / 83 (2.41%)  |  |
| occurrences (all)                 | 1               | 2               |  |

|   |                      |                        |  |
|---|----------------------|------------------------|--|
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all) | 0 / 12 (0.00%)<br>0  | 4 / 83 (4.82%)<br>4    |  |
| Metabolism and nutrition disorders  |                      |                        |  |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)      | 2 / 12 (16.67%)<br>2 | 12 / 83 (14.46%)<br>13 |  |
| Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all)          | 0 / 12 (0.00%)<br>0  | 2 / 83 (2.41%)<br>3    |  |
| Hypomagnesaemia<br>subjects affected / exposed<br>occurrences (all)         | 1 / 12 (8.33%)<br>1  | 5 / 83 (6.02%)<br>5    |  |
| Hyponatraemia<br>subjects affected / exposed<br>occurrences (all)           | 0 / 12 (0.00%)<br>0  | 7 / 83 (8.43%)<br>8    |  |
| Hyperkalaemia<br>subjects affected / exposed<br>occurrences (all)           | 0 / 12 (0.00%)<br>0  | 3 / 83 (3.61%)<br>4    |  |
| Hypoalbuminaemia<br>subjects affected / exposed<br>occurrences (all)        | 0 / 12 (0.00%)<br>0  | 3 / 83 (3.61%)<br>6    |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment   |
|-----------------|---|
| 21 October 2014 | The primary reasons for amendment 1 were to incorporate input from regulatory authorities, changed the length of the trial from 2.5 to 3 years, MK-3475 was changed to pembrolizumab, optional KRAS testing was removed, total administration of pembrolizumab was changed from 2 years to 35 cycles and the second course was limited to 1 year. |
| 28 January 2016 | The primary reason for amendment 3 was to incorporate an addition of an interim efficacy analysis for an external DMC review.   |
| 02 August 2016  | The primary reason for amendment 6 was the removal of the requirement for documented disease progression in order to crossover to pembrolizumab.  |
| 18 January 2018 | The primary reasons for amendment 9 was to allow flexibility of survival status activities and to provide current, comprehensive guidelines for the management of immune-related adverse events.  |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported