



## Clinical trial results:

### A Phase III Study of Pembrolizumab (MK-3475) vs. Best Supportive Care as Second-Line Therapy in Subjects With Previously Systemically Treated Advanced Hepatocellular Carcinoma (KEYNOTE-240)

#### Summary

|                          |                            |
|--------------------------|----------------------------|
| EudraCT number           | 2015-004567-36             |
| Trial protocol           | IE DE DK HU FR GB PL BE IT |
| Global end of trial date | 22 September 2021          |

#### Results information

|                                |                   |
|--------------------------------|-------------------|
| Result version number          | v1 (current)      |
| This version publication date  | 15 September 2022 |
| First version publication date | 15 September 2022 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 3475-240 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |                                       |
|------------------------------------|---------------------------------------|
| ISRCTN number                      | -                                     |
| ClinicalTrials.gov id (NCT number) | NCT02702401                           |
| WHO universal trial number (UTN)   | -                                     |
| Other trial identifiers            | JAPIC-CTI: 163456, Merck: KEYNOTE-240 |

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                       | 22 September 2021 |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 02 January 2019   |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 22 September 2021 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

This is a study of pembrolizumab (MK-3475) in participants with previously systemically treated advanced hepatocellular carcinoma (HCC).

The primary objectives of this study are to determine 1) Progression-Free Survival (PFS) and 2) Overall Survival (OS) of pembrolizumab plus best supportive care (BSC) compared with placebo plus BSC. The primary hypotheses of this study are: 1) pembrolizumab plus BSC prolongs PFS per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, assessed by Blinded Independent Central Review compared to placebo plus BSC, and 2) pembrolizumab plus BSC improves OS compared with placebo plus BSC.

Effective with Amendment 4: Upon study completion, participants are discontinued and may be enrolled in a pembrolizumab extension study, if available.

Protection of trial subjects:

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

Background therapy:

Background therapy will consist of best supportive care and will be administered to all arms in this study. Best supportive care will include pain management and management of other potential complications including ascites per local standards of care.

Evidence for comparator: -

|   |             |
|---|-------------|
| Actual start date of recruitment                          | 26 May 2016 |
| 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 | Argentina: 2  |
| Country: Number of subjects enrolled | Australia: 11 |
| Country: Number of subjects enrolled | Belgium: 11   |
| Country: Number of subjects enrolled | Canada: 1     |
| Country: Number of subjects enrolled | Chile: 8      |
| Country: Number of subjects enrolled | Colombia: 3   |
| Country: Number of subjects enrolled | Denmark: 5    |
| Country: Number of subjects enrolled | France: 78    |
| Country: Number of subjects enrolled | Germany: 10   |
| Country: Number of subjects enrolled | Hong Kong: 14 |
| Country: Number of subjects enrolled | Hungary: 11   |

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Ireland: 3             |
| Country: Number of subjects enrolled | Israel: 8              |
| Country: Number of subjects enrolled | Italy: 7               |
| Country: Number of subjects enrolled | Japan: 59              |
| Country: Number of subjects enrolled | Korea, Republic of: 50 |
| Country: Number of subjects enrolled | Mexico: 7              |
| Country: Number of subjects enrolled | Norway: 6              |
| Country: Number of subjects enrolled | Philippines: 2         |
| Country: Number of subjects enrolled | Poland: 5              |
| Country: Number of subjects enrolled | Russian Federation: 17 |
| Country: Number of subjects enrolled | Taiwan: 27             |
| Country: Number of subjects enrolled | Thailand: 5            |
| Country: Number of subjects enrolled | Turkey: 17             |
| Country: Number of subjects enrolled | United Kingdom: 9      |
| Country: Number of subjects enrolled | United States: 37      |
| Worldwide total number of subjects   | 413                    |
| EEA total number of subjects         | 136                    |

Notes:

### Subjects enrolled per age group

|   |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 173 |
| From 65 to 84 years                       | 233 |
| 85 years and over                         | 7   |

## Subject disposition

### Recruitment

Recruitment details:

Although 278 participants were randomized to receive pembrolizumab and 135 to receive placebo, 1 participant in the placebo group received pembrolizumab in error. The efficacy population included all participants as randomized and the safety population was adjusted to account for actual treatment received (pembrolizumab = 279, placebo = 134).

### Pre-assignment

Screening details:

Per protocol, response/progression or adverse events during the second pembrolizumab course were not counted towards efficacy outcome measures or safety outcome measures.

### Period 1

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

### Arms

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

Arm description:

Participants received pembrolizumab 200 mg by intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 35 cycles of treatment PLUS best supportive care (BSC). Participants who complete 35 administrations or achieve a complete response (CR) but progress after discontinuation can initiate a second course of pembrolizumab for up to 17 cycles (approximately 1 additional year).

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

Dosage and administration details:

200 mg on Day 1 of each 3-week cycle.

|                  |                                |
|------------------|--------------------------------|
| <b>Arm title</b> | Placebo + Best Supportive Care |
|------------------|--------------------------------|

Arm description:

Participants received placebo by IV infusion on Day 1 of each 3-week cycle for up to 35 cycles of treatment PLUS BSC.

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

Dosage and administration details:

0.90% w/v sodium chloride

| Number of subjects in period 1 | Pembrolizumab + Best Supportive Care | Placebo + Best Supportive Care |
|--------------------------------|--------------------------------------|--------------------------------|
|                                |                                      |                                |
| Started                        | 278                                  | 135                            |
| Treated                        | 278                                  | 135                            |
| Received second course         | 7                                    | 0                              |
| Completed                      | 0                                    | 0                              |
| Not completed                  | 278                                  | 135                            |
| Consent withdrawn by subject   | 15                                   | 5                              |
| Physician decision             | 1                                    | 2                              |
| Death                          | 242                                  | 125                            |
| Sponsor Decision               | 19                                   | 3                              |
| Lost to follow-up              | 1                                    | -                              |

## Baseline characteristics

### Reporting groups

|  |                                      |
|--|--------------------------------------|
| Reporting group title  | Pembrolizumab + Best Supportive Care |
| Reporting group description:   |                                      |
| Participants received pembrolizumab 200 mg by intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 35 cycles of treatment PLUS best supportive care (BSC). Participants who complete 35 administrations or achieve a complete response (CR) but progress after discontinuation can initiate a second course of pembrolizumab for up to 17 cycles (approximately 1 additional year). |                                      |
| Reporting group title  | Placebo + Best Supportive Care       |
| Reporting group description:   |                                      |
| Participants received placebo by IV infusion on Day 1 of each 3-week cycle for up to 35 cycles of treatment PLUS BSC.  |                                      |

| Reporting group values                             | Pembrolizumab + Best Supportive Care | Placebo + Best Supportive Care | Total |
|--|--------------------------------------|--------------------------------|-------|
| Number of subjects                                 | 278                                  | 135                            | 413   |
| 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)                               | 109                                  | 64                             | 173   |
| From 65-84 years                                   | 164                                  | 69                             | 233   |
| 85 years and over                                  | 5                                    | 2                              | 7     |
| Age Continuous                                     |                                      |                                |       |
| Units: Years                                       |                                      |                                |       |
| arithmetic mean                                    | 65.6                                 | 64.4                           | -     |
| standard deviation                                 | ± 11.1                               | ± 10.3                         |       |
| Sex: Female, Male                                  |                                      |                                |       |
| Units: Participants                                |                                      |                                |       |
| Female   | 52                                   | 23                             | 75    |
| Male   | 226                                  | 112                            | 338   |
| Race (NIH/OMB)                                     |                                      |                                |       |
| Units: Subjects                                    |                                      |                                |       |
| American Indian or Alaska Native                   | 5                                    | 1                              | 6     |
| Asian  | 113                                  | 52                             | 165   |
| Native Hawaiian or Other Pacific Islander          | 1                                    | 0                              | 1     |
| Black or African American                          | 13                                   | 6                              | 19    |
| White  | 143                                  | 70                             | 213   |
| More than one race                                 | 3                                    | 5                              | 8     |
| Unknown or Not Reported                            | 0                                    | 1                              | 1     |
| Ethnicity (NIH/OMB)                                |                                      |                                |       |
| Units: Subjects                                    |                                      |                                |       |
| Hispanic or Latino                                 | 22                                   | 13                             | 35    |

|   |     |     |     |
|---|-----|-----|-----|
| Not Hispanic or Latino  | 233 | 113 | 346 |
| Unknown or Not Reported   | 23  | 9   | 32  |
| Region of enrollment  |     |     |     |
| Units: Subjects   |     |     |     |
| Asia without Japan  | 67  | 31  | 98  |
| European Union  | 96  | 43  | 139 |
| Japan   | 40  | 19  | 59  |
| United States   | 21  | 16  | 37  |
| Others  | 54  | 26  | 80  |
| Macrovascular invasion  |     |     |     |
| The presence or absence of macrovascular invasion was obtained from case report forms.  |     |     |     |
| Units: Subjects   |     |     |     |
| Yes (Present)   | 36  | 16  | 52  |
| No (Absent)   | 242 | 119 | 361 |
| Alpha-fetoprotein level   |     |     |     |
| Alpha-fetoprotein levels were measured using an enzyme-linked immunosorbent assay (ELISA) and participants were categorized by those having alpha-fetoprotein levels of <200 ng/mL and those having levels of ≥200 ng/mL. |     |     |     |
| Units: Subjects   |     |     |     |
| <200 ng/mL  | 149 | 77  | 226 |
| ≥200 ng/mL  | 129 | 58  | 187 |

## End points

### End points reporting groups

|  |                                      |
|--|--------------------------------------|
| Reporting group title  | Pembrolizumab + Best Supportive Care |
| Reporting group description:<br>Participants received pembrolizumab 200 mg by intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 35 cycles of treatment PLUS best supportive care (BSC). Participants who complete 35 administrations or achieve a complete response (CR) but progress after discontinuation can initiate a second course of pembrolizumab for up to 17 cycles (approximately 1 additional year). |                                      |
| Reporting group title  | Placebo + Best Supportive Care       |
| Reporting group description:<br>Participants received placebo by IV infusion on Day 1 of each 3-week cycle for up to 35 cycles of treatment PLUS BSC.  |                                      |
| Subject analysis set title   | Pembrolizumab + Best Supportive Care |
| Subject analysis set type  | Safety analysis                      |
| Subject analysis set description:<br>Participants received pembrolizumab 200 mg by IV infusion on Day 1 of each 3-week cycle for up to 35 cycles of treatment PLUS BSC. Participants who complete 35 administrations or achieve a complete response (CR) but progress after discontinuation can initiate a second course of pembrolizumab for up to 17 cycles (approximately 1 additional year).                                 |                                      |
| Subject analysis set title   | Placebo + Best Supportive Care       |
| Subject analysis set type  | Safety analysis                      |
| Subject analysis set description:<br>Participants received placebo by IV infusion on Day 1 of each 3-week cycle for up to 35 cycles of treatment PLUS BSC.   |                                      |

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

|  |   |
|--|---|
| End point title  | Progression-Free Survival (PFS) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) |
| End point description:<br>PFS was defined as the time from randomization to the first documented progressive disease (PD) or death due to any cause, whichever occurred first, per RECIST 1.1 as assessed by Blinded Independent Central Review (BICR). PD was defined as ≥20% increase in the sum of diameters of target lesions and an absolute increase of ≥5 mm. The appearance of ≥1 new lesion was also considered PD. If there was no disease progression or death, participants were censored at the date of their last disease assessment. The PFS was analyzed using the product-limit (Kaplan-Meier) method for censored data. Final analyses for PFS was performed for the first pembrolizumab course at protocol specified cut off of 26-Mar-2018. The analysis population included all randomized participants. Participants were included in the treatment group to which they were randomized. |   |
| End point type   | Primary   |
| End point timeframe:<br>Through database cutoff date of 26-Mar-2018 (Up to approximately 21 months)  |   |

| End point values                 | Pembrolizumab + Best Supportive Care | Placebo + Best Supportive Care |  |  |
|----------------------------------|--------------------------------------|--------------------------------|--|--|
| Subject group type               | Reporting group                      | Reporting group                |  |  |
| Number of subjects analysed      | 278                                  | 135                            |  |  |
| Units: Months                    |                                      |                                |  |  |
| median (confidence interval 95%) | 3.0 (2.8 to 4.1)                     | 2.8 (2.5 to 4.1)               |  |  |



## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | PFS Hazard Ratio  |
| Statistical analysis description:<br>Cox regression model with Efron's method (treatment as covariate) stratified by geographic region, macrovascular invasion and alfa-fetoprotein level |   |
| Comparison groups   | Pembrolizumab + Best Supportive Care v Placebo + Best Supportive Care |
| Number of subjects included in analysis   | 413   |
| Analysis specification  | Pre-specified   |
| Analysis type   | superiority   |
| P-value   | = 0.0186 <sup>[1]</sup>   |
| Method  | Logrank   |
| Parameter estimate  | Hazard ratio (HR)   |
| Point estimate  | 0.775   |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | 0.609   |
| upper limit   | 0.987   |

Notes:

[1] - One-sided p-value stratified by geographic region, macrovascular invasion and alfa-fetoprotein level.

## Primary: Overall Survival (OS)

|   |                       |
|---|-----------------------|
| End point title   | Overall Survival (OS) |
| End point description:<br>OS was determined for all participants and was defined as the time from randomization to death due to any cause. Participants were censored at the date of their last follow-up. The OS was analyzed using the product-limit (Kaplan-Meier) method for censored data. Final analyses for OS was performed for the first pembrolizumab course at protocol specified cut off of 02-Jan-2019. The analysis population included all randomized participants. Participants were included in the treatment group to which they were randomized. |                       |
| End point type  | Primary               |
| End point timeframe:<br>Through database cutoff date of 02-Jan-2019 (Up to approximately 30 months)   |                       |

| End point values                 | Pembrolizumab + Best Supportive Care | Placebo + Best Supportive Care |  |  |
|----------------------------------|--------------------------------------|--------------------------------|--|--|
| Subject group type               | Reporting group                      | Reporting group                |  |  |
| Number of subjects analysed      | 278                                  | 135                            |  |  |
| Units: Months                    |                                      |                                |  |  |
| median (confidence interval 95%) | 13.9 (11.6 to 16.0)                  | 10.6 (8.3 to 13.5)             |  |  |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | OS Hazard Ratio   |
| Statistical analysis description:<br>Cox regression model with Efron's method (treatment as covariate) stratified by geographic region, macrovascular invasion and alfa-fetoprotein level |   |
| Comparison groups   | Pembrolizumab + Best Supportive Care v Placebo + Best Supportive Care |
| Number of subjects included in analysis   | 413   |
| Analysis specification  | Pre-specified   |
| Analysis type   | superiority   |
| P-value   | = 0.0238 <sup>[2]</sup>   |
| Method  | Logrank   |
| Parameter estimate  | Hazard ratio (HR)   |
| Point estimate  | 0.781   |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | 0.611   |
| upper limit   | 0.998   |

Notes:

[2] - One-sided p-value stratified by geographic region, macrovascular invasion and alfa-fetoprotein level.

## Secondary: Objective Response Rate (ORR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

|  |   |
|--|---|
| End point title  | Objective Response Rate (ORR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) |
| End point description:<br>ORR was determined in all participants and was defined as the percentage of participants who had a confirmed 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) per RECIST 1.1 as assessed by Blinded Independent Central Review (BICR). Participants with missing data were considered non-responders. The ORR was analyzed using the Miettinen & Nurminen method. The percentage of participants who experienced a CR or PR per RECIST 1.1 is presented. Final analyses for ORR was performed for the first pembrolizumab course at protocol specified cut off of 02-Jan-2019. The analysis population included all randomized participants. Participants were included in the treatment group to which they were randomized. |   |
| End point type   | Secondary   |
| End point timeframe:<br>Through database cutoff date of 02-Jan-2019 (Up to approximately 30 months)  |   |

| <b>End point values</b>           | Pembrolizumab + Best Supportive Care | Placebo + Best Supportive Care |  |  |
|-----------------------------------|--------------------------------------|--------------------------------|--|--|
| Subject group type                | Reporting group                      | Reporting group                |  |  |
| Number of subjects analysed       | 278                                  | 135                            |  |  |
| Units: Percentage of participants |                                      |                                |  |  |
| number (confidence interval 95%)  | 18.3 (14.0 to 23.4)                  | 4.4 (1.6 to 9.4)               |  |  |

## Statistical analyses

| <b>Statistical analysis title</b>   | ORR Difference in Percent   |
|---|---|
| Statistical analysis description:<br>Miettinen & Nurminen method stratified by geographic region, macrovascular invasion and alfa-fetoprotein level |   |
| Comparison groups   | Pembrolizumab + Best Supportive Care v Placebo + Best Supportive Care |
| Number of subjects included in analysis   | 413   |
| Analysis specification  | Pre-specified   |
| Analysis type   | other   |
| Parameter estimate  | Difference in Percent   |
| Point estimate  | 13.8  |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | 7.7   |
| upper limit   | 19.5  |

## Secondary: Disease Control Rate (DCR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

| <b>End point title</b>   | Disease Control Rate (DCR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) |
|--|--|
| End point description:<br>DCR was defined as the percentage of participants who had a Complete Response (CR: Disappearance of all target lesions), Partial Response (PR: $\geq 30\%$ decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters), or Stable Disease (SD) per RECIST 1.1 after $\geq 6$ weeks as assessed by Blinded Independent Central Review (BICR). The DCR was analyzed using the Miettinen & Nurminen method. The percentage of participants who experienced a CR, PR, or SD is presented. Final analyses for DCR was performed for the first pembrolizumab course at protocol specified cut off of 02-Jan-2019. The analysis population included all randomized participants. Participants were included in the treatment group to which they were randomized. |  |
| End point type   | Secondary  |
| End point timeframe:<br>Through database cutoff date of 02-Jan-2019 (Up to approximately 30 months)  |  |

| End point values                  | Pembrolizumab + Best Supportive Care | Placebo + Best Supportive Care |  |  |
|-----------------------------------|--------------------------------------|--------------------------------|--|--|
| Subject group type                | Reporting group                      | Reporting group                |  |  |
| Number of subjects analysed       | 278                                  | 135                            |  |  |
| Units: Percentage of participants |                                      |                                |  |  |
| number (confidence interval 95%)  | 62.2 (56.2 to 68.0)                  | 53.3 (44.6 to 62.0)            |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Progression (TTP) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

|  |   |
|--|---|
| End point title  | Time to Progression (TTP) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) |
| End point description:   |   |
| TTP was defined as the time from randomization to the first documented disease progression per RECIST 1.1 as assessed by Blinded Independent Central Review (BICR). PD was defined as $\geq 20\%$ increase in the sum of diameters of target lesions and an absolute increase of $\geq 5$ mm. The appearance of $\geq 1$ new lesion was also considered PD. If there was no documented disease progression, TTP was censored at last tumor assessment date. The TTP was analyzed using the product-limit (Kaplan-Meier) method for censored data. TTP per RECIST 1.1 is presented for all participants. Final analyses for TTP was performed for the first pembrolizumab course at protocol specified cut off of 02-Jan-2019. The analysis population included all randomized participants. Participants were included in the treatment group to which they were randomized. |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| Through database cutoff date of 02-Jan-2019 (Up to approximately 30 months)  |   |

| End point values                 | Pembrolizumab + Best Supportive Care | Placebo + Best Supportive Care |  |  |
|----------------------------------|--------------------------------------|--------------------------------|--|--|
| Subject group type               | Reporting group                      | Reporting group                |  |  |
| Number of subjects analysed      | 278                                  | 135                            |  |  |
| Units: Months                    |                                      |                                |  |  |
| median (confidence interval 95%) | 3.8 (2.8 to 4.4)                     | 2.8 (1.6 to 2.9)               |  |  |

## Statistical analyses

|  |   |
|--|---|
| Statistical analysis title   | TTP Hazard Ratio  |
| Statistical analysis description:  |   |
| Cox regression model with Efron's method (treatment as covariate) stratified by geographic region, macrovascular invasion and alfa-fetoprotein level |   |
| Comparison groups  | Pembrolizumab + Best Supportive Care v Placebo + Best Supportive Care |

|   |                   |
|---|-------------------|
| Number of subjects included in analysis | 413               |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | other             |
| P-value                                 | = 0.0011 [3]      |
| Method                                  | Logrank           |
| Parameter estimate                      | Hazard ratio (HR) |
| Point estimate                          | 0.688             |
| Confidence interval                     |                   |
| level                                   | 95 %              |
| sides                                   | 2-sided           |
| lower limit                             | 0.54              |
| upper limit                             | 0.877             |

Notes:

[3] - One-sided p-value stratified by geographic region, macrovascular invasion and alfa-fetoprotein level.

### Secondary: Duration of Response (DOR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

|                 |  |
|-----------------|--|
| End point title | Duration of Response (DOR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) |
|-----------------|--|

End point description:

In participants with a Complete Response (CR: disappearance of all target lesions) or Partial Response (PR:  $\geq 30\%$  decrease in sum of diameters of target lesions) per RECIST 1.1 by BICR, DOR was the time from first CR/PR until progressive disease (PD:  $\geq 20\%$  increase in the sum of diameters and an absolute increase of  $\geq 5$  mm; appearance of  $\geq 1$  new lesion is also PD) or death. Participants who did not progress or die at time of analysis were censored at last tumor assessment. Final analysis for DOR was done for the first pembrolizumab course at protocol specified cut off of 02-Jan-2019. The analysis population was all randomized participants who demonstrated at least a partial response. Participants were included in the treatment group to which they were randomized. "9999" indicates median and upper limit were not reached according to the prespecified methodology in the protocol.

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

End point timeframe:

From time of first documented evidence of CR or PR through database cutoff date of 02-Jan-2019 (Up to approximately 30 months)

| End point values                 | Pembrolizumab + Best Supportive Care | Placebo + Best Supportive Care |  |  |
|----------------------------------|--------------------------------------|--------------------------------|--|--|
| Subject group type               | Reporting group                      | Reporting group                |  |  |
| Number of subjects analysed      | 51                                   | 6                              |  |  |
| Units: Months                    |                                      |                                |  |  |
| median (confidence interval 95%) | 13.8 (6.9 to 9999)                   | 9999 (2.8 to 9999)             |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants Who Experienced At Least One Adverse Event (AE)

|  |  |
|--|--|
| End point title  | Number of Participants Who Experienced At Least One Adverse Event (AE) |
| End point description:   |  |
| An AE was defined as any untoward medical occurrence in a participant given a study treatment and not necessarily have to have a causal relationship with this treatment. An AE can thus be any unfavorable, unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the study treatment or protocol-specified procedure. Also worsening of a pre-existing condition temporally associated with the use of study treatment, was an AE. The number of participants who experienced at least one AE is presented. Final analyses for AE was performed for the first pembrolizumab course at protocol specified cut off of 02-Jan-2019. The analysis population included participants who received $\geq 1$ dose of study treatment. Participants were grouped by actual treatment received. |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| Through database cutoff date of 02-Jan-2019 (Up to approximately 30 months)  |  |

| End point values            | Pembrolizumab + Best Supportive Care | Placebo + Best Supportive Care |  |  |
|-----------------------------|--------------------------------------|--------------------------------|--|--|
| Subject group type          | Subject analysis set                 | Subject analysis set           |  |  |
| Number of subjects analysed | 279                                  | 134                            |  |  |
| Units: Participants         | 269                                  | 121                            |  |  |

## Statistical analyses

No statistical analyses for this end point

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

|  |  |
|--|--|
| End point title  | Number of Participants Who Discontinued Study Treatment Due to an Adverse Event (AE) |
| End point description:   |  |
| An AE was defined as any untoward medical occurrence in a participant given a study treatment and not necessarily have to have a causal relationship with this treatment. An AE can thus be any unfavorable, unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the study treatment or protocol-specified procedure. Also worsening of a pre-existing condition temporally associated with the use of study treatment, was an AE. The number of participants who discontinued study treatment due to an AE is presented. Final analyses for AE was performed for the first pembrolizumab course at protocol specified cut off of 02-Jan-2019. The analysis population included participants who received $\geq 1$ dose of study treatment. Participants were grouped by actual treatment received. |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| From Day 1 through end of treatment (Up to approximately 24 months)  |  |

| <b>End point values</b>     | Pembrolizumab<br>+ Best<br>Supportive<br>Care | Placebo + Best<br>Supportive<br>Care |  |  |
|-----------------------------|---|--------------------------------------|--|--|
| Subject group type          | Subject analysis set                          | Subject analysis set                 |  |  |
| Number of subjects analysed | 279   | 134                                  |  |  |
| Units: Participants         | 48  | 12                                   |  |  |

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Through database cutoff date of 22-Sep-2021 (Up to approximately 59.3 months).

Adverse event reporting additional description:

All participants who received  $\geq 1$  dose of study treatment. Per protocol, MedDRA terms "Neoplasm progression (NP)", "Malignant NP" & "Disease progression" unrelated to study drug are excluded as AEs. Due to a dosing error, the population for all-cause mortality and AEs was adjusted to account for actual treatment received.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 24.0 |
|--------------------|------|

### Reporting groups

|                       |                                      |
|-----------------------|--------------------------------------|
| Reporting group title | Pembrolizumab + Best Supportive Care |
|-----------------------|--------------------------------------|

Reporting group description:

Participants received pembrolizumab 200 mg by IV infusion on Day 1 of each 3-week cycle for up to 35 cycles of treatment PLUS BSC. Participants who complete 35 administrations or achieve a complete response (CR) but progress after discontinuation can initiate a second course of pembrolizumab for up to 17 cycles (approximately 1 additional year).

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

Reporting group description:

Participants who completed the first course of up to 35 administrations of pembrolizumab (~2 years) but progressed after discontinuation, initiated a second course of pembrolizumab at the investigator's discretion, at the same dose and schedule at 200 mg IV on Day 1 of each 3-week cycle (Q3W) for up to 17 cycles (up to ~1 year).

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | Placebo + Best Supportive Care |
|-----------------------|--------------------------------|

Reporting group description:

Participants received placebo by IV infusion on Day 1 of each 3-week cycle for up to 35 cycles of treatment PLUS BSC.

| Serious adverse events  | Pembrolizumab + Best Supportive Care | Pembrolizumab Second Course | Placebo + Best Supportive Care |
|---|--------------------------------------|-----------------------------|--------------------------------|
| Total subjects affected by serious adverse events                   |                                      |                             |                                |
| subjects affected / exposed   | 106 / 279 (37.99%)                   | 3 / 7 (42.86%)              | 37 / 134 (27.61%)              |
| number of deaths (all causes)                                       | 246                                  | 3                           | 124                            |
| number of deaths resulting from adverse events                      | 1                                    | 1                           | 0                              |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                      |                             |                                |
| Adenocarcinoma of colon   |                                      |                             |                                |
| subjects affected / exposed   | 1 / 279 (0.36%)                      | 0 / 7 (0.00%)               | 0 / 134 (0.00%)                |
| occurrences causally related to treatment / all                     | 0 / 1                                | 0 / 0                       | 0 / 0                          |
| deaths causally related to treatment / all                          | 0 / 0                                | 0 / 0                       | 0 / 0                          |
| Gastric cancer  |                                      |                             |                                |



|  |                 |               |                 |
|--|-----------------|---------------|-----------------|
| subjects affected / exposed                          | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (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           |
| Insulinoma   |                 |               |                 |
| subjects affected / exposed                          | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (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                          | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (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           |
| Oral neoplasm  |                 |               |                 |
| subjects affected / exposed                          | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (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           |
| Tumour haemorrhage                                   |                 |               |                 |
| subjects affected / exposed                          | 0 / 279 (0.00%) | 0 / 7 (0.00%) | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0         | 0 / 0           |
| Tumour rupture                                       |                 |               |                 |
| subjects affected / exposed                          | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0         | 0 / 0           |
| Vascular disorders                                   |                 |               |                 |
| Aortic stenosis                                      |                 |               |                 |
| subjects affected / exposed                          | 0 / 279 (0.00%) | 0 / 7 (0.00%) | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0         | 0 / 0           |
| Hypotension  |                 |               |                 |
| subjects affected / exposed                          | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (0.00%) |
| occurrences causally related to treatment / all      | 1 / 1           | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0         | 0 / 0           |
| General disorders and administration site conditions |                 |               |                 |

|   |                 |               |                 |
|---|-----------------|---------------|-----------------|
| Chest pain                                      |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (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           |
| Death   |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0         | 0 / 1           |
| Fatigue   |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| General physical health deterioration           |                 |               |                 |
| subjects affected / exposed                     | 2 / 279 (0.72%) | 0 / 7 (0.00%) | 0 / 134 (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           |
| Influenza like illness                          |                 |               |                 |
| subjects affected / exposed                     | 0 / 279 (0.00%) | 0 / 7 (0.00%) | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Mucosal inflammation                            |                 |               |                 |
| subjects affected / exposed                     | 0 / 279 (0.00%) | 0 / 7 (0.00%) | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Pyrexia   |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (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           |
| Immune system disorders                         |                 |               |                 |
| Contrast media allergy                          |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (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           |
| Respiratory, thoracic and mediastinal           |                 |               |                 |

|   |                 |               |                 |
|---|-----------------|---------------|-----------------|
| disorders                                       |                 |               |                 |
| Chronic obstructive pulmonary disease           |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (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           |
| Dyspnoea  |                 |               |                 |
| subjects affected / exposed                     | 0 / 279 (0.00%) | 0 / 7 (0.00%) | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Haemoptysis                                     |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Interstitial lung disease                       |                 |               |                 |
| subjects affected / exposed                     | 3 / 279 (1.08%) | 0 / 7 (0.00%) | 0 / 134 (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           |
| Pleural effusion                                |                 |               |                 |
| subjects affected / exposed                     | 2 / 279 (0.72%) | 0 / 7 (0.00%) | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Pleurisy  |                 |               |                 |
| subjects affected / exposed                     | 0 / 279 (0.00%) | 0 / 7 (0.00%) | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Pneumonitis                                     |                 |               |                 |
| subjects affected / exposed                     | 2 / 279 (0.72%) | 0 / 7 (0.00%) | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0         | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Pneumothorax                                    |                 |               |                 |
| subjects affected / exposed                     | 2 / 279 (0.72%) | 0 / 7 (0.00%) | 0 / 134 (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           |

|   |                 |               |                 |
|---|-----------------|---------------|-----------------|
| Psychiatric disorders                           |                 |               |                 |
| Mental status changes                           |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (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           |
| Investigations                                  |                 |               |                 |
| Alanine aminotransferase increased              |                 |               |                 |
| subjects affected / exposed                     | 7 / 279 (2.51%) | 0 / 7 (0.00%) | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all | 5 / 7           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Aspartate aminotransferase increased            |                 |               |                 |
| subjects affected / exposed                     | 9 / 279 (3.23%) | 0 / 7 (0.00%) | 4 / 134 (2.99%) |
| occurrences causally related to treatment / all | 5 / 9           | 0 / 0         | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Blood bilirubin increased                       |                 |               |                 |
| subjects affected / exposed                     | 8 / 279 (2.87%) | 0 / 7 (0.00%) | 2 / 134 (1.49%) |
| occurrences causally related to treatment / all | 3 / 8           | 0 / 0         | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Blood creatinine increased                      |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Injury, poisoning and procedural complications  |                 |               |                 |
| Fall  |                 |               |                 |
| subjects affected / exposed                     | 0 / 279 (0.00%) | 0 / 7 (0.00%) | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Femoral neck fracture                           |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (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           |
| Femur fracture                                  |                 |               |                 |

|   |                 |               |                 |
|---|-----------------|---------------|-----------------|
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Hip fracture                                    |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Humerus fracture                                |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (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           |
| Ligament sprain                                 |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (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           |
| Lumbar vertebral fracture                       |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (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 procedure complication                 |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (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                               |                 |               |                 |
| Atrial fibrillation                             |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 2 / 134 (1.49%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0         | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Cardiac arrest                                  |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (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           |
| Myocardial infarction                           |                 |               |                 |

|   |                 |               |                 |
|---|-----------------|---------------|-----------------|
| subjects affected / exposed                     | 2 / 279 (0.72%) | 0 / 7 (0.00%) | 0 / 134 (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           |
| Myocardial ischaemia                            |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 1           |
| Pericardial effusion                            |                 |               |                 |
| subjects affected / exposed                     | 0 / 279 (0.00%) | 0 / 7 (0.00%) | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Supraventricular tachycardia                    |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Nervous system disorders                        |                 |               |                 |
| Cerebral infarction                             |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Cerebrovascular accident                        |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (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           |
| Hepatic encephalopathy                          |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Seizure   |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (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           |
| Syncope   |                 |               |                 |

|   |                 |               |                 |
|---|-----------------|---------------|-----------------|
| subjects affected / exposed                     | 0 / 279 (0.00%) | 0 / 7 (0.00%) | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| <b>Blood and lymphatic system disorders</b>     |                 |               |                 |
| Anaemia   |                 |               |                 |
| subjects affected / exposed                     | 3 / 279 (1.08%) | 0 / 7 (0.00%) | 5 / 134 (3.73%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0         | 1 / 6           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Immune thrombocytopenia                         |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (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           |
| Thrombocytopenia                                |                 |               |                 |
| subjects affected / exposed                     | 0 / 279 (0.00%) | 0 / 7 (0.00%) | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| <b>Eye disorders</b>                            |                 |               |                 |
| Blindness unilateral                            |                 |               |                 |
| subjects affected / exposed                     | 0 / 279 (0.00%) | 0 / 7 (0.00%) | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Macular hole                                    |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (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           |
| Retinal detachment                              |                 |               |                 |
| subjects affected / exposed                     | 0 / 279 (0.00%) | 0 / 7 (0.00%) | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Retinal vein occlusion                          |                 |               |                 |
| subjects affected / exposed                     | 0 / 279 (0.00%) | 0 / 7 (0.00%) | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| <b>Gastrointestinal disorders</b>               |                 |               |                 |

|   |                  |                |                 |
|---|------------------|----------------|-----------------|
| Abdominal distension                            |                  |                |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%)  | 0 / 7 (0.00%)  | 0 / 134 (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           |
| Abdominal pain                                  |                  |                |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%)  | 0 / 7 (0.00%)  | 0 / 134 (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           |
| Abdominal pain upper                            |                  |                |                 |
| subjects affected / exposed                     | 2 / 279 (0.72%)  | 0 / 7 (0.00%)  | 0 / 134 (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           |
| Ascites   |                  |                |                 |
| subjects affected / exposed                     | 13 / 279 (4.66%) | 0 / 7 (0.00%)  | 5 / 134 (3.73%) |
| occurrences causally related to treatment / all | 1 / 14           | 0 / 0          | 0 / 5           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0           |
| Colitis   |                  |                |                 |
| subjects affected / exposed                     | 2 / 279 (0.72%)  | 1 / 7 (14.29%) | 0 / 134 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2            | 1 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0            | 1 / 1          | 0 / 0           |
| Constipation                                    |                  |                |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%)  | 0 / 7 (0.00%)  | 0 / 134 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0           |
| Diarrhoea                                       |                  |                |                 |
| subjects affected / exposed                     | 2 / 279 (0.72%)  | 0 / 7 (0.00%)  | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0           |
| Diverticular fistula                            |                  |                |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%)  | 0 / 7 (0.00%)  | 0 / 134 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0           |
| Diverticulum intestinal haemorrhagic            |                  |                |                 |



|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%)  | 0 / 134 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Gastric ulcer                                   |                 |                |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%)  | 0 / 134 (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           |
| Gastritis                                       |                 |                |                 |
| subjects affected / exposed                     | 0 / 279 (0.00%) | 0 / 7 (0.00%)  | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Gastroduodenal ulcer                            |                 |                |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%)  | 0 / 134 (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           |
| Gastrointestinal haemorrhage                    |                 |                |                 |
| subjects affected / exposed                     | 0 / 279 (0.00%) | 1 / 7 (14.29%) | 0 / 134 (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           |
| Gastrointestinal inflammation                   |                 |                |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%)  | 0 / 134 (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           |
| Intestinal obstruction                          |                 |                |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%)  | 0 / 134 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Intestinal perforation                          |                 |                |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%)  | 0 / 134 (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           |
| Intra-abdominal haemorrhage                     |                 |                |                 |

|   |                 |               |                 |
|---|-----------------|---------------|-----------------|
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Oesophageal varices haemorrhage                 |                 |               |                 |
| subjects affected / exposed                     | 3 / 279 (1.08%) | 0 / 7 (0.00%) | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0         | 0 / 0           |
| Small intestinal obstruction                    |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Upper gastrointestinal haemorrhage              |                 |               |                 |
| subjects affected / exposed                     | 3 / 279 (1.08%) | 0 / 7 (0.00%) | 0 / 134 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0         | 0 / 0           |
| Varices oesophageal                             |                 |               |                 |
| subjects affected / exposed                     | 3 / 279 (1.08%) | 0 / 7 (0.00%) | 0 / 134 (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           |
| Vomiting  |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (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           |
| Hepatobiliary disorders                         |                 |               |                 |
| Autoimmune hepatitis                            |                 |               |                 |
| subjects affected / exposed                     | 2 / 279 (0.72%) | 0 / 7 (0.00%) | 0 / 134 (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           |
| Cholangitis                                     |                 |               |                 |
| subjects affected / exposed                     | 0 / 279 (0.00%) | 0 / 7 (0.00%) | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Cholestasis                                     |                 |               |                 |

|   |                 |               |                 |
|---|-----------------|---------------|-----------------|
| subjects affected / exposed                     | 2 / 279 (0.72%) | 0 / 7 (0.00%) | 0 / 134 (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           |
| Hepatic cirrhosis                               |                 |               |                 |
| subjects affected / exposed                     | 2 / 279 (0.72%) | 0 / 7 (0.00%) | 0 / 134 (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           |
| Hepatic cyst                                    |                 |               |                 |
| subjects affected / exposed                     | 0 / 279 (0.00%) | 0 / 7 (0.00%) | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Hepatic failure                                 |                 |               |                 |
| subjects affected / exposed                     | 2 / 279 (0.72%) | 0 / 7 (0.00%) | 2 / 134 (1.49%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0         | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 1           |
| Hepatic haemorrhage                             |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Hyperbilirubinaemia                             |                 |               |                 |
| subjects affected / exposed                     | 2 / 279 (0.72%) | 0 / 7 (0.00%) | 0 / 134 (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           |
| Immune-mediated hepatitis                       |                 |               |                 |
| subjects affected / exposed                     | 3 / 279 (1.08%) | 0 / 7 (0.00%) | 0 / 134 (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           |
| Jaundice  |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (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           |
| Jaundice cholestatic                            |                 |               |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%)  | 0 / 134 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Skin and subcutaneous tissue disorders          |                 |                |                 |
| Erythema multiforme                             |                 |                |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%)  | 0 / 134 (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           |
| Lichenoid keratosis                             |                 |                |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%)  | 0 / 134 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Renal and urinary disorders                     |                 |                |                 |
| Acute kidney injury                             |                 |                |                 |
| subjects affected / exposed                     | 3 / 279 (1.08%) | 0 / 7 (0.00%)  | 0 / 134 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Nephrolithiasis                                 |                 |                |                 |
| subjects affected / exposed                     | 0 / 279 (0.00%) | 0 / 7 (0.00%)  | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Renal failure                                   |                 |                |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%)  | 0 / 134 (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           |
| Endocrine disorders                             |                 |                |                 |
| Hypophysitis                                    |                 |                |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%)  | 0 / 134 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Hypothyroidism                                  |                 |                |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 1 / 7 (14.29%) | 0 / 134 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| Musculoskeletal and connective tissue disorders |                 |                |                 |
| Arthralgia                                      |                 |                |                 |
| subjects affected / exposed                     | 0 / 279 (0.00%) | 0 / 7 (0.00%)  | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Back pain                                       |                 |                |                 |
| subjects affected / exposed                     | 0 / 279 (0.00%) | 1 / 7 (14.29%) | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Bursitis  |                 |                |                 |
| subjects affected / exposed                     | 0 / 279 (0.00%) | 0 / 7 (0.00%)  | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Lumbar spinal stenosis                          |                 |                |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%)  | 0 / 134 (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           |
| Neck pain                                       |                 |                |                 |
| subjects affected / exposed                     | 0 / 279 (0.00%) | 0 / 7 (0.00%)  | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Osteochondrosis                                 |                 |                |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%)  | 0 / 134 (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           |
| Pain in extremity                               |                 |                |                 |
| subjects affected / exposed                     | 0 / 279 (0.00%) | 1 / 7 (14.29%) | 0 / 134 (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           |
| Pathological fracture                           |                 |                |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%)  | 0 / 134 (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           |

|   |                 |               |                 |
|---|-----------------|---------------|-----------------|
| Polymyalgia rheumatica                          |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Infections and infestations                     |                 |               |                 |
| Bronchitis                                      |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (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 / 279 (0.36%) | 0 / 7 (0.00%) | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Gastroenteritis                                 |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (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           |
| Hepatitis B                                     |                 |               |                 |
| subjects affected / exposed                     | 0 / 279 (0.00%) | 0 / 7 (0.00%) | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Hepatitis C                                     |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (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           |
| Infection                                       |                 |               |                 |
| subjects affected / exposed                     | 2 / 279 (0.72%) | 0 / 7 (0.00%) | 0 / 134 (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           |
| Influenza                                       |                 |               |                 |
| subjects affected / exposed                     | 0 / 279 (0.00%) | 0 / 7 (0.00%) | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Liver abscess                                   |                 |               |                 |

|   |                 |               |                 |
|---|-----------------|---------------|-----------------|
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Mycobacterial infection                         |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (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           |
| Peritonitis                                     |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 1           |
| Peritonitis bacterial                           |                 |               |                 |
| subjects affected / exposed                     | 2 / 279 (0.72%) | 0 / 7 (0.00%) | 0 / 134 (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           |
| Pleural infection                               |                 |               |                 |
| subjects affected / exposed                     | 0 / 279 (0.00%) | 0 / 7 (0.00%) | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Pneumonia                                       |                 |               |                 |
| subjects affected / exposed                     | 6 / 279 (2.15%) | 0 / 7 (0.00%) | 3 / 134 (2.24%) |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 0         | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Pneumonia bacterial                             |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Pneumonia mycoplasmal                           |                 |               |                 |
| subjects affected / exposed                     | 0 / 279 (0.00%) | 0 / 7 (0.00%) | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Sepsis  |                 |               |                 |

|   |                 |               |                 |
|---|-----------------|---------------|-----------------|
| subjects affected / exposed                     | 2 / 279 (0.72%) | 0 / 7 (0.00%) | 0 / 134 (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           |
| Thrombophlebitis septic                         |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Upper respiratory tract infection               |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Urinary tract infection                         |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Metabolism and nutrition disorders              |                 |               |                 |
| Decreased appetite                              |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (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           |
| Dehydration                                     |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (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                     | 0 / 279 (0.00%) | 0 / 7 (0.00%) | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Hypercalcaemia                                  |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0         | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Hyperglycaemia                                  |                 |               |                 |



|   |                 |               |                 |
|---|-----------------|---------------|-----------------|
| subjects affected / exposed                     | 0 / 279 (0.00%) | 0 / 7 (0.00%) | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |
| Hyperkalaemia                                   |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (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           |
| Hypoglycaemia                                   |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 0 / 134 (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           |
| Type 1 diabetes mellitus                        |                 |               |                 |
| subjects affected / exposed                     | 1 / 279 (0.36%) | 0 / 7 (0.00%) | 1 / 134 (0.75%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0         | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0         | 0 / 0           |

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

| <b>Non-serious adverse events</b>                     | <b>Pembrolizumab + Best Supportive Care</b> | <b>Pembrolizumab Second Course</b> | <b>Placebo + Best Supportive Care</b> |
|---|---|------------------------------------|---------------------------------------|
| Total subjects affected by non-serious adverse events |   |                                    |                                       |
| subjects affected / exposed                           | 240 / 279 (86.02%)                          | 7 / 7 (100.00%)                    | 109 / 134 (81.34%)                    |
| Vascular disorders                                    |   |                                    |                                       |
| Hypertension  |   |                                    |                                       |
| subjects affected / exposed                           | 10 / 279 (3.58%)                            | 0 / 7 (0.00%)                      | 8 / 134 (5.97%)                       |
| occurrences (all)                                     | 10  | 0                                  | 14                                    |
| General disorders and administration site conditions  |   |                                    |                                       |
| Asthenia  |   |                                    |                                       |
| subjects affected / exposed                           | 26 / 279 (9.32%)                            | 0 / 7 (0.00%)                      | 15 / 134 (11.19%)                     |
| occurrences (all)                                     | 35  | 0                                  | 17                                    |
| Fatigue   |   |                                    |                                       |
| subjects affected / exposed                           | 51 / 279 (18.28%)                           | 2 / 7 (28.57%)                     | 31 / 134 (23.13%)                     |
| occurrences (all)                                     | 60  | 2                                  | 32                                    |
| Oedema peripheral                                     |   |                                    |                                       |

|   |                   |                |                   |
|---|-------------------|----------------|-------------------|
| subjects affected / exposed                     | 32 / 279 (11.47%) | 1 / 7 (14.29%) | 17 / 134 (12.69%) |
| occurrences (all)                               | 39                | 1              | 20                |
| Pyrexia   |                   |                |                   |
| subjects affected / exposed                     | 25 / 279 (8.96%)  | 0 / 7 (0.00%)  | 15 / 134 (11.19%) |
| occurrences (all)                               | 27                | 0              | 22                |
| Reproductive system and breast disorders        |                   |                |                   |
| Penile erythema                                 |                   |                |                   |
| subjects affected / exposed                     | 1 / 279 (0.36%)   | 1 / 7 (14.29%) | 0 / 134 (0.00%)   |
| occurrences (all)                               | 2                 | 1              | 0                 |
| Respiratory, thoracic and mediastinal disorders |                   |                |                   |
| Cough   |                   |                |                   |
| subjects affected / exposed                     | 24 / 279 (8.60%)  | 1 / 7 (14.29%) | 24 / 134 (17.91%) |
| occurrences (all)                               | 32                | 1              | 27                |
| Dyspnoea  |                   |                |                   |
| subjects affected / exposed                     | 19 / 279 (6.81%)  | 0 / 7 (0.00%)  | 14 / 134 (10.45%) |
| occurrences (all)                               | 19                | 0              | 16                |
| Nasal congestion                                |                   |                |                   |
| subjects affected / exposed                     | 2 / 279 (0.72%)   | 1 / 7 (14.29%) | 1 / 134 (0.75%)   |
| occurrences (all)                               | 2                 | 1              | 2                 |
| Rhinorrhoea                                     |                   |                |                   |
| subjects affected / exposed                     | 1 / 279 (0.36%)   | 1 / 7 (14.29%) | 3 / 134 (2.24%)   |
| occurrences (all)                               | 1                 | 1              | 3                 |
| Psychiatric disorders                           |                   |                |                   |
| Sleep disorder                                  |                   |                |                   |
| subjects affected / exposed                     | 1 / 279 (0.36%)   | 1 / 7 (14.29%) | 0 / 134 (0.00%)   |
| occurrences (all)                               | 1                 | 1              | 0                 |
| Insomnia  |                   |                |                   |
| subjects affected / exposed                     | 12 / 279 (4.30%)  | 0 / 7 (0.00%)  | 8 / 134 (5.97%)   |
| occurrences (all)                               | 12                | 0              | 10                |
| Investigations                                  |                   |                |                   |
| Alanine aminotransferase increased              |                   |                |                   |
| subjects affected / exposed                     | 45 / 279 (16.13%) | 0 / 7 (0.00%)  | 12 / 134 (8.96%)  |
| occurrences (all)                               | 49                | 0              | 12                |
| Aspartate aminotransferase increased            |                   |                |                   |

|  |                   |                |                   |
|--|-------------------|----------------|-------------------|
| subjects affected / exposed                    | 55 / 279 (19.71%) | 0 / 7 (0.00%)  | 18 / 134 (13.43%) |
| occurrences (all)                              | 58                | 0              | 21                |
| Blood alkaline phosphatase increased           |                   |                |                   |
| subjects affected / exposed                    | 20 / 279 (7.17%)  | 0 / 7 (0.00%)  | 9 / 134 (6.72%)   |
| occurrences (all)                              | 20                | 0              | 9                 |
| Gamma-glutamyltransferase increased            |                   |                |                   |
| subjects affected / exposed                    | 18 / 279 (6.45%)  | 0 / 7 (0.00%)  | 7 / 134 (5.22%)   |
| occurrences (all)                              | 19                | 0              | 7                 |
| Blood bilirubin increased                      |                   |                |                   |
| subjects affected / exposed                    | 46 / 279 (16.49%) | 0 / 7 (0.00%)  | 16 / 134 (11.94%) |
| occurrences (all)                              | 59                | 0              | 18                |
| Platelet count decreased                       |                   |                |                   |
| subjects affected / exposed                    | 13 / 279 (4.66%)  | 1 / 7 (14.29%) | 2 / 134 (1.49%)   |
| occurrences (all)                              | 16                | 1              | 2                 |
| Injury, poisoning and procedural complications |                   |                |                   |
| Procedural pain                                |                   |                |                   |
| subjects affected / exposed                    | 3 / 279 (1.08%)   | 1 / 7 (14.29%) | 0 / 134 (0.00%)   |
| occurrences (all)                              | 3                 | 1              | 0                 |
| Nervous system disorders                       |                   |                |                   |
| Headache                                       |                   |                |                   |
| subjects affected / exposed                    | 20 / 279 (7.17%)  | 0 / 7 (0.00%)  | 5 / 134 (3.73%)   |
| occurrences (all)                              | 23                | 0              | 7                 |
| Blood and lymphatic system disorders           |                   |                |                   |
| Anaemia  |                   |                |                   |
| subjects affected / exposed                    | 27 / 279 (9.68%)  | 0 / 7 (0.00%)  | 11 / 134 (8.21%)  |
| occurrences (all)                              | 29                | 0              | 18                |
| Lymphadenopathy                                |                   |                |                   |
| subjects affected / exposed                    | 1 / 279 (0.36%)   | 1 / 7 (14.29%) | 1 / 134 (0.75%)   |
| occurrences (all)                              | 1                 | 1              | 1                 |
| Gastrointestinal disorders                     |                   |                |                   |
| Abdominal pain                                 |                   |                |                   |
| subjects affected / exposed                    | 39 / 279 (13.98%) | 0 / 7 (0.00%)  | 9 / 134 (6.72%)   |
| occurrences (all)                              | 51                | 0              | 9                 |
| Abdominal pain upper                           |                   |                |                   |
| subjects affected / exposed                    | 25 / 279 (8.96%)  | 0 / 7 (0.00%)  | 10 / 134 (7.46%)  |
| occurrences (all)                              | 27                | 0              | 14                |

|  |                   |                |                   |
|--|-------------------|----------------|-------------------|
| Ascites                                |                   |                |                   |
| subjects affected / exposed            | 15 / 279 (5.38%)  | 0 / 7 (0.00%)  | 8 / 134 (5.97%)   |
| occurrences (all)                      | 15                | 0              | 8                 |
| Constipation                           |                   |                |                   |
| subjects affected / exposed            | 28 / 279 (10.04%) | 0 / 7 (0.00%)  | 15 / 134 (11.19%) |
| occurrences (all)                      | 33                | 0              | 16                |
| Diarrhoea                              |                   |                |                   |
| subjects affected / exposed            | 49 / 279 (17.56%) | 0 / 7 (0.00%)  | 20 / 134 (14.93%) |
| occurrences (all)                      | 74                | 0              | 24                |
| Gastrooesophageal reflux disease       |                   |                |                   |
| subjects affected / exposed            | 5 / 279 (1.79%)   | 1 / 7 (14.29%) | 2 / 134 (1.49%)   |
| occurrences (all)                      | 6                 | 1              | 2                 |
| Nausea                                 |                   |                |                   |
| subjects affected / exposed            | 33 / 279 (11.83%) | 0 / 7 (0.00%)  | 20 / 134 (14.93%) |
| occurrences (all)                      | 41                | 0              | 21                |
| Toothache                              |                   |                |                   |
| subjects affected / exposed            | 3 / 279 (1.08%)   | 1 / 7 (14.29%) | 0 / 134 (0.00%)   |
| occurrences (all)                      | 4                 | 1              | 0                 |
| Pneumatosis intestinalis               |                   |                |                   |
| subjects affected / exposed            | 0 / 279 (0.00%)   | 1 / 7 (14.29%) | 0 / 134 (0.00%)   |
| occurrences (all)                      | 0                 | 1              | 0                 |
| Vomiting                               |                   |                |                   |
| subjects affected / exposed            | 26 / 279 (9.32%)  | 0 / 7 (0.00%)  | 5 / 134 (3.73%)   |
| occurrences (all)                      | 41                | 0              | 9                 |
| Skin and subcutaneous tissue disorders |                   |                |                   |
| Pruritus                               |                   |                |                   |
| subjects affected / exposed            | 53 / 279 (19.00%) | 0 / 7 (0.00%)  | 17 / 134 (12.69%) |
| occurrences (all)                      | 66                | 0              | 18                |
| Rash                                   |                   |                |                   |
| subjects affected / exposed            | 35 / 279 (12.54%) | 0 / 7 (0.00%)  | 7 / 134 (5.22%)   |
| occurrences (all)                      | 42                | 0              | 8                 |
| Renal and urinary disorders            |                   |                |                   |
| Dysuria                                |                   |                |                   |
| subjects affected / exposed            | 2 / 279 (0.72%)   | 1 / 7 (14.29%) | 1 / 134 (0.75%)   |
| occurrences (all)                      | 2                 | 1              | 1                 |
| Endocrine disorders                    |                   |                |                   |

|  |                         |                     |                         |
|--|-------------------------|---------------------|-------------------------|
| Hypothyroidism<br>subjects affected / exposed<br>occurrences (all)     | 13 / 279 (4.66%)<br>14  | 0 / 7 (0.00%)<br>0  | 7 / 134 (5.22%)<br>7    |
| Musculoskeletal and connective tissue disorders                        |                         |                     |                         |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)         | 33 / 279 (11.83%)<br>37 | 0 / 7 (0.00%)<br>0  | 17 / 134 (12.69%)<br>19 |
| Back pain<br>subjects affected / exposed<br>occurrences (all)          | 29 / 279 (10.39%)<br>31 | 0 / 7 (0.00%)<br>0  | 13 / 134 (9.70%)<br>14  |
| Neck pain<br>subjects affected / exposed<br>occurrences (all)          | 4 / 279 (1.43%)<br>4    | 1 / 7 (14.29%)<br>1 | 0 / 134 (0.00%)<br>0    |
| Flank pain<br>subjects affected / exposed<br>occurrences (all)         | 5 / 279 (1.79%)<br>8    | 1 / 7 (14.29%)<br>1 | 3 / 134 (2.24%)<br>3    |
| Infections and infestations  |                         |                     |                         |
| Herpes zoster<br>subjects affected / exposed<br>occurrences (all)      | 2 / 279 (0.72%)<br>2    | 1 / 7 (14.29%)<br>1 | 0 / 134 (0.00%)<br>0    |
| Metabolism and nutrition disorders                                     |                         |                     |                         |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all) | 47 / 279 (16.85%)<br>51 | 0 / 7 (0.00%)<br>0  | 21 / 134 (15.67%)<br>23 |
| Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all)     | 12 / 279 (4.30%)<br>21  | 0 / 7 (0.00%)<br>0  | 7 / 134 (5.22%)<br>7    |
| Hypoalbuminaemia<br>subjects affected / exposed<br>occurrences (all)   | 21 / 279 (7.53%)<br>25  | 0 / 7 (0.00%)<br>0  | 7 / 134 (5.22%)<br>7    |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date           | Amendment  |
|----------------|--|
| 09 March 2016  | The primary reason for amendment 1 was removal of health economic assessment (HEA) from patient reported outcomes, removal of the option of including participants without confirmed diagnosis of HCC from inclusion criterion, removal of "target lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions" from inclusion criterion and insertion of clarifying text 'negative for anti-HBs' (Hepatitis B surface antibody) to exclusion criteria. Other primary reasons included updates and corrections to prohibited concomitant medications, supportive care guidelines, participant withdrawal/discontinuation criteria, trial flow charts, investigational products and the appendix. |
| 03 August 2016 | The primary reason for amendment 2 was addition of participant eligibility by radiographic diagnosis for HCC and text to change percentage of participants to be enrolled in the specified populations and countries.  |
| 16 March 2017  | The primary reason for amendment 3 was addition of 2nd interim analysis, updates to show survival status activities taking place throughout the trial and addition of "the trial will be deemed positive if either OS or PFS null hypothesis are rejected" to the primary objectives and hypothesis. Other primary reasons included updates and corrections to survival follow-up phase, dose modification guidelines and survival status.   |
| 03 March 2021  | The primary reason for amendment 4 was addition of language to include the requirement of roll over of trial participants into an extension trial (if available) when this trial is completed, update to assessment by radiologic imaging from every 6 weeks (Q6W) to every 12 weeks (Q12W) and duration of follow-up phase.   |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported