



## Clinical trial results:

### A Phase III, Open-Label, Multicenter, Two Arm, Randomized Study to Investigate the Efficacy and Safety of Cobimetinib Plus Atezolizumab Versus Pembrolizumab in Patients With Previously Untreated Advanced BRAF V600 Wild-Type Melanoma

#### Summary

|                          |                               |
|--------------------------|-------------------------------|
| EudraCT number           | 2016-004387-18                |
| Trial protocol           | DE NL BE HU PL GB ES GR FR IT |
| Global end of trial date |                               |

#### Results information

|                                |             |
|--------------------------------|-------------|
| Result version number          | v1          |
| This version publication date  | 01 May 2020 |
| First version publication date | 01 May 2020 |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | CO39722 |
|-----------------------|---------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03273153 |
| WHO universal trial number (UTN)   | -           |

Notes:

##### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Hoffmann-La Roche  |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, 4070  |
| Public contact               | Medical Communications, Hoffmann-La Roche, +41 616878333, global.trial_information@roche.com |
| Scientific contact           | Medical Communications, Hoffmann-La Roche, +41 616878333, global.trial_information@roche.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                                       | Interim       |
| Date of interim/final analysis                       | 15 April 2019 |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 15 April 2019 |
| Global end of trial reached?                         | No            |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the efficacy, safety, and pharmacokinetics of cobimetinib plus atezolizumab compared with pembrolizumab in treatment-naïve participants with advanced BRAFV600 wild-type melanoma.

Protection of trial subjects:

All participants were required to sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 11 December 2017 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Australia: 9           |
| Country: Number of subjects enrolled | Brazil: 14             |
| Country: Number of subjects enrolled | Korea, Republic of: 9  |
| Country: Number of subjects enrolled | Belgium: 12            |
| Country: Number of subjects enrolled | France: 59             |
| Country: Number of subjects enrolled | Germany: 29            |
| Country: Number of subjects enrolled | Greece: 25             |
| Country: Number of subjects enrolled | Hungary: 15            |
| Country: Number of subjects enrolled | Italy: 64              |
| Country: Number of subjects enrolled | Netherlands: 6         |
| Country: Number of subjects enrolled | Poland: 36             |
| Country: Number of subjects enrolled | Russian Federation: 60 |
| Country: Number of subjects enrolled | Spain: 39              |
| Country: Number of subjects enrolled | United Kingdom: 20     |
| Country: Number of subjects enrolled | United States: 49      |
| Worldwide total number of subjects   | 446                    |
| EEA total number of subjects         | 305                    |

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)                      | 202 |
| From 65 to 84 years                       | 237 |
| 85 years and over                         | 7   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Treatment-naïve adult participants with advanced BRAFV600 wild-type melanoma.

### Period 1

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

### Arms

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

Arm description:

Participants received 200 mg of intravenous (IV) pembrolizumab every 3 weeks (Q3W) until investigator-determined disease progression, unacceptable toxicity, death, patient or physician decision to withdraw, or pregnancy, whichever occurred first.

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

Dosage and administration details:

Participants received 200 mg of IV pembrolizumab once every 3 weeks.

|                  |                              |
|------------------|------------------------------|
| <b>Arm title</b> | Cobimetinib and Atezolizumab |
|------------------|------------------------------|

Arm description:

Participants received 60 mg of cobimetinib by mouth (PO) on a 21 days on, 7 days off schedule (dosing on Days 1-21, followed by no dosing on Days 22-28) plus 840 mg of atezolizumab by IV infusion of Days 1 and 15 of each 28-day cycle.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Cobimetinib  |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Participants received 60 mg of oral cobimetinib once daily on a 21 days on, 7 days off schedule.

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

Dosage and administration details:

Participants received 840 mg of IV atezolizumab once every 2 weeks.

| <b>Number of subjects in period 1</b> | Pembrolizumab | Cobimetinib and Atezolizumab |
|---------------------------------------|---------------|------------------------------|
| Started                               | 224           | 222                          |
| Completed                             | 0             | 0                            |
| Not completed                         | 224           | 222                          |
| Adverse event, serious fatal          | 41            | 45                           |
| Consent withdrawn by subject          | 16            | 13                           |
| Remain on Study                       | 161           | 159                          |
| Unspecified                           | -             | 1                            |
| Symptomatic Deterioration             | -             | 1                            |
| Lost to follow-up                     | 3             | 3                            |
| Protocol deviation                    | 3             | -                            |

## Baseline characteristics

### Reporting groups

|  |                              |
|--|------------------------------|
| Reporting group title  | Pembrolizumab                |
| Reporting group description:<br>Participants received 200 mg of intravenous (IV) pembrolizumab every 3 weeks (Q3W) until investigator-determined disease progression, unacceptable toxicity, death, patient or physician decision to withdraw, or pregnancy, whichever occurred first. |                              |
| Reporting group title  | Cobimetinib and Atezolizumab |
| Reporting group description:<br>Participants received 60 mg of cobimetinib by mouth (PO) on a 21 days on, 7 days off schedule (dosing on Days 1-21, followed by no dosing on Days 22-28) plus 840 mg of atezolizumab by IV infusion of Days 1 and 15 of each 28-day cycle.             |                              |

| Reporting group values                    | Pembrolizumab | Cobimetinib and Atezolizumab | Total |
|---|---------------|------------------------------|-------|
| Number of subjects                        | 224           | 222                          | 446   |
| Age categorical<br>Units: Subjects        |               |                              |       |
| Adults (18-64 years)                      | 100           | 102                          | 202   |
| From 65-84 years                          | 122           | 115                          | 237   |
| 85 years and over                         | 2             | 5                            | 7     |
| Age Continuous<br>Units: Years            |               |                              |       |
| arithmetic mean                           | 63.5          | 63.6                         |       |
| standard deviation                        | ± 12.9        | ± 13.1                       | -     |
| Sex: Female, Male<br>Units:               |               |                              |       |
| Female                                    | 83            | 93                           | 176   |
| Male                                      | 141           | 129                          | 270   |
| Race (NIH/OMB)<br>Units: Subjects         |               |                              |       |
| American Indian or Alaska Native          | 0             | 0                            | 0     |
| Asian                                     | 6             | 6                            | 12    |
| Native Hawaiian or Other Pacific Islander | 0             | 0                            | 0     |
| Black or African American                 | 1             | 6                            | 7     |
| White                                     | 198           | 188                          | 386   |
| More than one race                        | 0             | 0                            | 0     |
| Unknown or Not Reported                   | 19            | 22                           | 41    |
| Ethnicity (NIH/OMB)<br>Units: Subjects    |               |                              |       |
| Hispanic or Latino                        | 7             | 15                           | 22    |
| Not Hispanic or Latino                    | 190           | 180                          | 370   |
| Unknown or Not Reported                   | 27            | 27                           | 54    |

## End points

### End points reporting groups

|  |                              |
|--|------------------------------|
| Reporting group title  | Pembrolizumab                |
| Reporting group description:<br>Participants received 200 mg of intravenous (IV) pembrolizumab every 3 weeks (Q3W) until investigator-determined disease progression, unacceptable toxicity, death, patient or physician decision to withdraw, or pregnancy, whichever occurred first. |                              |
| Reporting group title  | Cobimetinib and Atezolizumab |
| Reporting group description:<br>Participants received 60 mg of cobimetinib by mouth (PO) on a 21 days on, 7 days off schedule (dosing on Days 1-21, followed by no dosing on Days 22-28) plus 840 mg of atezolizumab by IV infusion of Days 1 and 15 of each 28-day cycle.             |                              |

### Primary: Progression Free Survival (PFS) as Determined by the Independent Review Committee (IRC)

|   |   |
|---|---|
| End point title   | Progression Free Survival (PFS) as Determined by the Independent Review Committee (IRC) |
| End point description:<br>PFS is defined as the time from randomization to the first occurrence of disease progression, as determined by an IRC according to RECIST v1.1, or death from any cause, whichever occurs first. Progressive disease (PD) for target lesion: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline). In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of $\geq 5$ mm. PD for non-target lesion: Unequivocal progression of existing non-target lesions. Tumor assessments, including contrast-enhanced CT or MRI scans, will be performed every 8 weeks (wks) from Day (D) 1 of Cycle (C) 1 through 80 wks and then every 12 wks thereafter, until confirmed disease progression or loss of clinical benefit, withdrawal of consent, study termination by the Sponsor or death, whichever occurs first. |   |
| End point type  | Primary   |
| End point timeframe:<br>Every 8 weeks (wks) from Day (D) 1 of Cycle (C) 1 through 80 wks and then every 12 wks thereafter   |   |

| End point values                 | Pembrolizumab    | Cobimetinib and Atezolizumab |  |  |
|----------------------------------|------------------|------------------------------|--|--|
| Subject group type               | Reporting group  | Reporting group              |  |  |
| Number of subjects analysed      | 224              | 222                          |  |  |
| Units: Months                    |                  |                              |  |  |
| median (confidence interval 95%) | 5.7 (3.7 to 9.6) | 5.5 (3.8 to 7.2)             |  |  |

### Statistical analyses

|                            |  |
|----------------------------|--|
| Statistical analysis title | PFS  |
| Comparison groups          | Pembrolizumab v Cobimetinib and Atezolizumab |

|   |                   |
|---|-------------------|
| Number of subjects included in analysis | 446               |
| Analysis specification                  | Pre-specified     |
| Analysis type                           |                   |
| P-value                                 | = 0.2954          |
| Method                                  | Regression, Cox   |
| Parameter estimate                      | Hazard ratio (HR) |
| Point estimate                          | 1.15              |
| Confidence interval                     |                   |
| level                                   | 95 %              |
| sides                                   | 2-sided           |
| lower limit                             | 0.88              |
| upper limit                             | 1.5               |

### Secondary: PFS as Determined by the Investigator

|   |                                       |
|---|---------------------------------------|
| End point title   | PFS as Determined by the Investigator |
| End point description:  |                                       |
| <p>PFS is defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first. Progressive disease (PD) for target lesion: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline). In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of <math>\geq 5</math> mm. PD for non-target lesion: Unequivocal progression of existing non-target lesions.</p> |                                       |
| End point type  | Secondary                             |
| End point timeframe:  |                                       |
| Every 8 weeks (wks) from Day (D) 1 of Cycle (C) 1 through 80 wks and then every 12 wks thereafter   |                                       |

| End point values                 | Pembrolizumab     | Cobimetinib and Atezolizumab |  |  |
|----------------------------------|-------------------|------------------------------|--|--|
| Subject group type               | Reporting group   | Reporting group              |  |  |
| Number of subjects analysed      | 224               | 222                          |  |  |
| Units: Months                    |                   |                              |  |  |
| median (confidence interval 95%) | 7.2 (3.8 to 10.1) | 5.6 (3.9 to 6.6)             |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Objective Response as Determined by the Investigator

|  |  |
|--|--|
| End point title  | Objective Response as Determined by the Investigator |
| End point description:   |  |
| <p>Objective response rate is defined as the percentage of participants with a complete response (CR) or a partial response (PR) on two consecutive occasions <math>\geq 4</math> weeks apart, as determined by the investigator through the use of RECIST v1.1. For target lesion, CR: the disappearance of all target lesions, any pathological lymph nodes must have a reduction in short axis to <math>&lt; 10</math> mm. PR: at least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of</p> |  |



diameters, in the absence of CR. For non-target lesion, CR: the disappearance of all non-target lesions and (if applicable) normalization of tumor marker level, all lymph nodes must be non-pathological in size (<10 mm short axis).

|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:  |           |
| Every 8 weeks (wks) from Day (D) 1 of Cycle (C) 1 through 80 wks and then every 12 wks thereafter |           |

| End point values                  | Pembrolizumab         | Cobimetinib and Atezolizumab |  |  |
|-----------------------------------|-----------------------|------------------------------|--|--|
| Subject group type                | Reporting group       | Reporting group              |  |  |
| Number of subjects analysed       | 221                   | 222                          |  |  |
| Units: Percentage of Participants |                       |                              |  |  |
| number (confidence interval 95%)  | 36.7 (30.29 to 43.38) | 27.9 (22.13 to 34.32)        |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Objective Response as Determined by IRC

|   |   |
|---|---|
| End point title   | Objective Response as Determined by IRC |
| End point description:  |   |
| Objective response, defined as a complete response or partial response on two consecutive occasions ≥4 weeks apart, as determined by IRC according to RECIST v1.1 |   |
| End point type  | Secondary                               |
| End point timeframe:  |   |
| Every 8 weeks (wks) from Day (D) 1 of Cycle (C) 1 through 80 wks and then every 12 wks thereafter   |   |

| End point values                  | Pembrolizumab         | Cobimetinib and Atezolizumab |  |  |
|-----------------------------------|-----------------------|------------------------------|--|--|
| Subject group type                | Reporting group       | Reporting group              |  |  |
| Number of subjects analysed       | 206                   | 204                          |  |  |
| Units: Percentage of Participants |                       |                              |  |  |
| number (confidence interval 95%)  | 31.6 (25.27 to 38.38) | 26.0 (20.11 to 32.57)        |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Disease Control Rate (DCR)

|                 |                            |
|-----------------|----------------------------|
| End point title | Disease Control Rate (DCR) |
|-----------------|----------------------------|

**End point description:**

DCR is defined as the proportion of participants with a complete response, a partial response, or stable disease at 16 weeks. For target lesion, CR: the disappearance of all target lesions, any pathological lymph nodes must have a reduction in short axis to <10 mm. PR: at least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR. For non-target lesion, CR: the disappearance of all non-target lesions and (if applicable) normalization of tumor marker level, all lymph nodes must be non-pathological in size (<10 mm short axis). Stable disease (SD): neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD.

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

**End point timeframe:**

Every 8 weeks (wks) from Day (D) 1 of Cycle (C) 1 through 80 wks and then every 12 wks thereafter

| End point values                  | Pembrolizumab         | Cobimetinib and Atezolizumab |  |  |
|-----------------------------------|-----------------------|------------------------------|--|--|
| Subject group type                | Reporting group       | Reporting group              |  |  |
| Number of subjects analysed       | 221                   | 222                          |  |  |
| Units: Percentage of Participants |                       |                              |  |  |
| number (confidence interval 95%)  |                       |                              |  |  |
| Investigator-assessed             | 49.8 (43.00 to 56.56) | 46.8 (40.14 to 53.64)        |  |  |
| IRC-assessed (n= 206, 204)        | 44.2 (37.28 to 51.24) | 45.6 (38.62 to 52.69)        |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Overall Survival (OS)**

|                 |                       |
|-----------------|-----------------------|
| End point title | Overall Survival (OS) |
|-----------------|-----------------------|

**End point description:**

OS is defined as the time from randomization to death from any cause.

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

**End point timeframe:**

Up to 7 years

| End point values                 | Pembrolizumab       | Cobimetinib and Atezolizumab |  |  |
|----------------------------------|---------------------|------------------------------|--|--|
| Subject group type               | Reporting group     | Reporting group              |  |  |
| Number of subjects analysed      | 224 <sup>[1]</sup>  | 222 <sup>[2]</sup>           |  |  |
| Units: Months                    |                     |                              |  |  |
| median (confidence interval 95%) | 9999 (9999 to 9999) | 9999 (13.0 to 9999)          |  |  |

**Notes:**

[1] - 9999 = value not available due to insufficient number of participants with event

## Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of objective response determined by the IRC

|                 |  |
|-----------------|--|
| End point title | Duration of objective response determined by the IRC |
|-----------------|--|

End point description:

Duration of objective response, defined as the time from the first occurrence of a documented objective response to disease progression, as determined by an IRC according to RECIST v1.1, or death from any cause, whichever occurs first.

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

End point timeframe:

Every 8 weeks (wks) from Day (D) 1 of Cycle (C) 1 through 80 wks and then every 12 wks thereafter

| End point values                 | Pembrolizumab       | Cobimetinib and Atezolizumab |  |  |
|----------------------------------|---------------------|------------------------------|--|--|
| Subject group type               | Reporting group     | Reporting group              |  |  |
| Number of subjects analysed      | 65 <sup>[3]</sup>   | 53 <sup>[4]</sup>            |  |  |
| Units: Months                    |                     |                              |  |  |
| median (confidence interval 95%) | 9999 (9999 to 9999) | 9999 (9.2 to 9999)           |  |  |

Notes:

[3] - 9999 = Values are not estimable due to an insufficient number of participants with the event.

[4] - 9999 = Values are not estimable due to an insufficient number of participants with the event.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of Objective Response determined by the Investigator

|                 |   |
|-----------------|---|
| End point title | Duration of Objective Response determined by the Investigator |
|-----------------|---|

End point description:

Duration of objective response is defined as the time from the first occurrence of a documented objective response to disease progression, as determined by the investigator through use of RECIST v1.1, or death from any cause, whichever occurs first.

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

End point timeframe:

Every 8 weeks (wks) from Day (D) 1 of Cycle (C) 1 through 80 wks and then every 12 wks thereafter

| End point values                 | Pembrolizumab       | Cobimetinib and Atezolizumab |  |  |
|----------------------------------|---------------------|------------------------------|--|--|
| Subject group type               | Reporting group     | Reporting group              |  |  |
| Number of subjects analysed      | 81 <sup>[5]</sup>   | 62 <sup>[6]</sup>            |  |  |
| Units: Months                    |                     |                              |  |  |
| median (confidence interval 95%) | 9999 (9999 to 9999) | 9999 (9.2 to 9999)           |  |  |

Notes:

[5] - 9999 = value not available due to insufficient number of participants with event

[6] - 9999 = value not available due to insufficient number of participants with event

## Statistical analyses

No statistical analyses for this end point

## Secondary: Two-year Landmark Survival

|                        |   |
|------------------------|---|
| End point title        | Two-year Landmark Survival                                    |
| End point description: | Two-year landmark survival is defined as survival at 2 years. |
| End point type         | Secondary   |
| End point timeframe:   | At 2 years  |

| End point values            | Pembrolizumab    | Cobimetinib and Atezolizumab |  |  |
|-----------------------------|------------------|------------------------------|--|--|
| Subject group type          | Reporting group  | Reporting group              |  |  |
| Number of subjects analysed | 0 <sup>[7]</sup> | 0 <sup>[8]</sup>             |  |  |
| Units: None                 |                  |                              |  |  |
| number (not applicable)     |                  |                              |  |  |

Notes:

[7] - Timeframe for endpoint has not yet been reached.

[8] - Timeframe for endpoint has not yet been reached.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Health-related Quality of Life (HRQoL) Scores

|                        |  |
|------------------------|--|
| End point title        | Change From Baseline in Health-related Quality of Life (HRQoL) Scores  |
| End point description: | HRQoL scores are assessed through global health status (GHS)/ quality of life (QoL) subscale of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ C30). These are based on questions 29 and 30 of the EORTC QLQ-C30. These questions on global health status/QoL scale are coded on 7-point scale (1=very poor to 7=excellent). Raw scores will be linearly transformed to obtain the score ranging from 0 to 100, where higher score represents a higher ("better") level of functioning. |
| End point type         | Secondary  |
| End point timeframe:   | Up to 7 years  |

| <b>End point values</b>              | Pembrolizumab      | Cobimetinib<br>and<br>Atezolizumab |  |  |
|--------------------------------------|--------------------|------------------------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group                    |  |  |
| Number of subjects analysed          | 174 <sup>[9]</sup> | 160 <sup>[10]</sup>                |  |  |
| Units: Units on a Scale              |                    |                                    |  |  |
| arithmetic mean (standard deviation) |                    |                                    |  |  |
| Baseline value                       | 73.27 (± 20.41)    | 73.85 (± 19.73)                    |  |  |
| Week 4                               | -2.99 (± 17.05)    | -9.14 (± 20.83)                    |  |  |
| Week 8                               | -3.15 (± 18.67)    | -5.21 (± 18.18)                    |  |  |
| Week 12                              | -1.77 (± 19.93)    | -7.65 (± 21.20)                    |  |  |
| Week 16                              | 1.16 (± 15.02)     | -6.44 (± 20.58)                    |  |  |
| Week 20                              | 1.69 (± 17.50)     | -6.31 (± 19.17)                    |  |  |
| Week 24                              | -1.84 (± 19.82)    | -2.49 (± 15.98)                    |  |  |
| Week 28                              | 2.46 (± 19.07)     | -3.86 (± 19.10)                    |  |  |
| Week 32                              | -0.88 (± 22.41)    | -4.66 (± 20.94)                    |  |  |
| Week 36                              | 4.17 (± 20.56)     | -6.00 (± 18.24)                    |  |  |
| Week 40                              | 7.22 (± 19.38)     | -4.63 (± 21.62)                    |  |  |
| Week 44                              | 0.46 (± 19.27)     | 1.67 (± 12.91)                     |  |  |
| Week 48                              | 7.64 (± 13.04)     | 0.00 (± 15.96)                     |  |  |
| Week 52                              | 1.67 (± 12.36)     | 8.33 (± 15.21)                     |  |  |
| Week 56                              | -11.11 (± 17.21)   | -2.08 (± 4.17)                     |  |  |
| Week 60                              | -8.33 (± 11.79)    | -4.17 (± 5.89)                     |  |  |
| Week 64                              | 33.33 (± 9999)     | 9999 (± 9999)                      |  |  |
| Treatment Discontinuation            | -6.05 (± 22.53)    | -14.42 (± 25.68)                   |  |  |
| Follow-up 4                          | -7.64 (± 14.85)    | -2.27 (± 18.67)                    |  |  |
| Follow-up 8                          | -14.25 (± 21.96)   | -14.10 (± 24.15)                   |  |  |
| Follow-up 12                         | -21.38 (± 24.34)   | -24.31 (± 28.08)                   |  |  |
| Follow-up 16                         | -13.73 (± 19.53)   | -23.61 (± 23.26)                   |  |  |
| Follow-up 20                         | -20.83 (± 26.53)   | -8.33 (± 12.91)                    |  |  |
| Follow-up 24                         | -17.71 (± 29.36)   | -10.00 (± 14.91)                   |  |  |
| Follow-up 28                         | -27.78 (± 22.15)   | -16.67 (± 23.57)                   |  |  |

Notes:

[9] - 9999 = value not available

[10] - 9999 = value not available

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants with Adverse Events (AEs)

|  |  |
|--|--|
| End point title  | Number of Participants with Adverse Events (AEs) |
| End point description:<br>An adverse event is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as adverse events. |  |
| End point type   | Secondary  |
| End point timeframe:<br>Up to 7 years  |  |

|                               |                 |                              |  |  |
|-------------------------------|-----------------|------------------------------|--|--|
| <b>End point values</b>       | Pembrolizumab   | Cobimetinib and Atezolizumab |  |  |
| Subject group type            | Reporting group | Reporting group              |  |  |
| Number of subjects analysed   | 216             | 220                          |  |  |
| Units: Number of Participants | 191             | 218                          |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants With Abnormal Vital Signs

|   |  |
|---|--|
| End point title   | Number of Participants With Abnormal Vital Signs |
| End point description:<br>Vital signs will include temperature pulse rate, respiratory rate, and systolic and diastolic blood pressure. |  |
| End point type  | Secondary  |
| End point timeframe:<br>Up to 7 years   |  |

| End point values              | Pembrolizumab     | Cobimetinib and Atezolizumab |  |  |
|-------------------------------|-------------------|------------------------------|--|--|
| Subject group type            | Reporting group   | Reporting group              |  |  |
| Number of subjects analysed   | 0 <sup>[11]</sup> | 0 <sup>[12]</sup>            |  |  |
| Units: Number of Participants |                   |                              |  |  |
| number (not applicable)       |                   |                              |  |  |

Notes:

[11] - Values not available at the time of primary results reporting.

[12] - Values not available at the time of primary results reporting.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With Laboratory Abnormalities

|                        |  |
|------------------------|--|
| End point title        | Number of Participants With Laboratory Abnormalities   |
| End point description: | Participants with laboratory abnormalities (values outside of a defined range) are reported. |
| End point type         | Secondary  |
| End point timeframe:   |  |
| Up to 7 years          |  |

| End point values                      | Pembrolizumab   | Cobimetinib and Atezolizumab |  |  |
|---------------------------------------|-----------------|------------------------------|--|--|
| Subject group type                    | Reporting group | Reporting group              |  |  |
| Number of subjects analysed           | 216             | 220                          |  |  |
| Units: Number of Participants         |                 |                              |  |  |
| SGPT/ALT                              | 1               | 1                            |  |  |
| Amylase (n= 201, 204)                 | 4               | 5                            |  |  |
| SGOT/AST (n= 215, 220)                | 0               | 2                            |  |  |
| Calcium                               | 0               | 1                            |  |  |
| Creatine Kinase (n= 215, 220)         | 1               | 17                           |  |  |
| Creatinine                            | 1               | 4                            |  |  |
| Glucose (n= 210, 218)                 | 8               | 13                           |  |  |
| Triacylglycerol Lipase (n= 197, 200)  | 8               | 10                           |  |  |
| Magnesium (n= 215, 217)               | 3               | 2                            |  |  |
| Phosphorus (n= 216, 217)              | 6               | 10                           |  |  |
| Potassium                             | 1               | 6                            |  |  |
| Sodium                                | 2               | 4                            |  |  |
| Uric Acid (n= 179, 188)               | 36              | 30                           |  |  |
| Hemoglobin                            | 2               | 2                            |  |  |
| Lymphocytes Abs (n= 173, 178)         | 6               | 15                           |  |  |
| Neutrophils, Total, Abs (n= 174, 179) | 0               | 1                            |  |  |
| Total Leukocyte Count                 | 3               | 0                            |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma Concentration of Cobimetinib

|                 |   |
|-----------------|---|
| End point title | Plasma Concentration of Cobimetinib <sup>[13]</sup> |
|-----------------|---|

End point description:

Plasma concentration of cobimetinib at specified time points will be reported.

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

End point timeframe:

Days 1 and 15 of Cycle 1

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is specific to the reported arm.

| End point values                     | Cobimetinib and Atezolizumab |  |  |  |
|--------------------------------------|------------------------------|--|--|--|
| Subject group type                   | Reporting group              |  |  |  |
| Number of subjects analysed          | 0 <sup>[14]</sup>            |  |  |  |
| Units: ng/mL                         |                              |  |  |  |
| arithmetic mean (standard deviation) | ( )                          |  |  |  |

Notes:

[14] - PK parameters will be reported with final results.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Serum Concentration of Atezolizumab

|                 |   |
|-----------------|---|
| End point title | Serum Concentration of Atezolizumab <sup>[15]</sup> |
|-----------------|---|

End point description:

Serum concentration of atezolizumab at specified time points will be reported.

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

End point timeframe:

Day 1 of Cycle 1, 2, 3 and 30 days after treatment discontinuation

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is specific to the reported arm.

| End point values            | Cobimetinib and Atezolizumab |  |  |  |
|-----------------------------|------------------------------|--|--|--|
| Subject group type          | Reporting group              |  |  |  |
| Number of subjects analysed | 0 <sup>[16]</sup>            |  |  |  |
| Units: none                 |                              |  |  |  |
| number (not applicable)     |                              |  |  |  |



Notes:

[16] - PK parameters will be reported with final results.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with Anti-drug Antibodies (ADAs)

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants with Anti-drug Antibodies (ADAs) <sup>[17]</sup> |
|-----------------|---|

End point description:

Participants with ADAs during the study relative to the prevalence of ADAs at baseline will be reported.

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

End point timeframe:

Day 1 of Cycle 1, 2, 3 and 30 days after treatment discontinuation

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is specific to the reported arm.

| End point values            | Cobimetinib and Atezolizumab |  |  |  |
|-----------------------------|------------------------------|--|--|--|
| Subject group type          | Reporting group              |  |  |  |
| Number of subjects analysed | 0 <sup>[18]</sup>            |  |  |  |
| Units: None                 |                              |  |  |  |
| number (not applicable)     |                              |  |  |  |

Notes:

[18] - PD parameters will be reported with final results.

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

For up to 135 days after the last dose of study drug, or until a new systemic anti-cancer therapy was initiated, whichever occurred first.

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 22.0   |

### Reporting groups

|                       |                              |
|-----------------------|------------------------------|
| Reporting group title | Cobimetinib and Atezolizumab |
|-----------------------|------------------------------|

Reporting group description:

Participants received 60 mg of cobimetinib by mouth (PO) on a 21 days on, 7 days off schedule (dosing on Days 1-21, followed by no dosing on Days 22-28) plus 840 mg of atezolizumab by IV infusion of Days 1 and 15 of each 28-day cycle.

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

Reporting group description:

Participants received 200 mg of IV pembrolizumab every 3 weeks (Q3W) until investigator-determined disease progression, unacceptable toxicity, death, patient or physician decision to withdraw, or pregnancy, whichever occurred first.

| Serious adverse events  | Cobimetinib and Atezolizumab | Pembrolizumab     |  |
|---|------------------------------|-------------------|--|
| Total subjects affected by serious adverse events                   |                              |                   |  |
| subjects affected / exposed   | 97 / 220 (44.09%)            | 45 / 216 (20.83%) |  |
| number of deaths (all causes)                                       | 45                           | 42                |  |
| number of deaths resulting from adverse events                      |                              |                   |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                              |                   |  |
| Prostate cancer   |                              |                   |  |
| subjects affected / exposed   | 1 / 220 (0.45%)              | 0 / 216 (0.00%)   |  |
| occurrences causally related to treatment / all                     | 0 / 1                        | 0 / 0             |  |
| deaths causally related to treatment / all                          | 0 / 0                        | 0 / 0             |  |
| Tumour haemorrhage  |                              |                   |  |
| subjects affected / exposed   | 0 / 220 (0.00%)              | 1 / 216 (0.46%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0                        | 0 / 1             |  |
| deaths causally related to treatment / all                          | 0 / 0                        | 0 / 0             |  |
| Tumour pain   |                              |                   |  |
| subjects affected / exposed   | 0 / 220 (0.00%)              | 1 / 216 (0.46%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0                        | 0 / 1             |  |
| deaths causally related to treatment / all                          | 0 / 0                        | 0 / 0             |  |

|  |                  |                 |  |
|--|------------------|-----------------|--|
| Vascular disorders                                   |                  |                 |  |
| Hypotension  |                  |                 |  |
| subjects affected / exposed                          | 1 / 220 (0.45%)  | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |
| Haematoma  |                  |                 |  |
| subjects affected / exposed                          | 1 / 220 (0.45%)  | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |
| Hypertension   |                  |                 |  |
| subjects affected / exposed                          | 0 / 220 (0.00%)  | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |
| Orthostatic hypotension                              |                  |                 |  |
| subjects affected / exposed                          | 1 / 220 (0.45%)  | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |
| General disorders and administration site conditions |                  |                 |  |
| Pyrexia  |                  |                 |  |
| subjects affected / exposed                          | 12 / 220 (5.45%) | 2 / 216 (0.93%) |  |
| occurrences causally related to treatment / all      | 0 / 12           | 0 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |
| Asthenia   |                  |                 |  |
| subjects affected / exposed                          | 4 / 220 (1.82%)  | 3 / 216 (1.39%) |  |
| occurrences causally related to treatment / all      | 0 / 4            | 0 / 3           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |
| Fatigue  |                  |                 |  |
| subjects affected / exposed                          | 3 / 220 (1.36%)  | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 3            | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |
| General physical health deterioration                |                  |                 |  |
| subjects affected / exposed                          | 1 / 220 (0.45%)  | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| Chest pain                                      |                   |                   |  |
| subjects affected / exposed                     | 0 / 220 (0.00%)   | 1 / 216 (0.46%)   |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Death   |                   |                   |  |
| subjects affected / exposed                     | 45 / 220 (20.45%) | 42 / 216 (19.44%) |  |
| occurrences causally related to treatment / all | 1 / 45            | 0 / 42            |  |
| deaths causally related to treatment / all      | 1 / 45            | 0 / 42            |  |
| Malaise   |                   |                   |  |
| subjects affected / exposed                     | 1 / 220 (0.45%)   | 0 / 216 (0.00%)   |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Multiple organ dysfunction syndrome             |                   |                   |  |
| subjects affected / exposed                     | 1 / 220 (0.45%)   | 0 / 216 (0.00%)   |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Non-cardiac chest pain                          |                   |                   |  |
| subjects affected / exposed                     | 1 / 220 (0.45%)   | 0 / 216 (0.00%)   |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Immune system disorders                         |                   |                   |  |
| Hypersensitivity                                |                   |                   |  |
| subjects affected / exposed                     | 1 / 220 (0.45%)   | 0 / 216 (0.00%)   |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Respiratory, thoracic and mediastinal disorders |                   |                   |  |
| Pulmonary embolism                              |                   |                   |  |
| subjects affected / exposed                     | 2 / 220 (0.91%)   | 4 / 216 (1.85%)   |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 4             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Dyspnoea  |                   |                   |  |
| subjects affected / exposed                     | 3 / 220 (1.36%)   | 2 / 216 (0.93%)   |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Haemoptysis                                     |                 |                 |  |
| subjects affected / exposed                     | 2 / 220 (0.91%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cough   |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Interstitial lung disease                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pleural effusion                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 220 (0.00%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Investigations                                  |                 |                 |  |
| Blood bilirubin increased                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 220 (0.91%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood creatine phosphokinase increased          |                 |                 |  |
| subjects affected / exposed                     | 2 / 220 (0.91%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood creatinine increased                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 220 (0.91%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Aspartate aminotransferase increased            |                 |                 |  |
| subjects affected / exposed                     | 2 / 220 (0.91%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| Alanine aminotransferase increased<br>subjects affected / exposed  | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to<br>treatment / all                 | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                      | 0 / 0           | 0 / 0           |  |
| General physical condition abnormal<br>subjects affected / exposed | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to<br>treatment / all                 | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                      | 0 / 0           | 0 / 0           |  |
| Transaminases increased<br>subjects affected / exposed             | 0 / 220 (0.00%) | 1 / 216 (0.46%) |  |
| occurrences causally related to<br>treatment / all                 | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                      | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural<br>complications                  |                 |                 |  |
| Infusion related reaction<br>subjects affected / exposed           | 3 / 220 (1.36%) | 0 / 216 (0.00%) |  |
| occurrences causally related to<br>treatment / all                 | 0 / 3           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                      | 0 / 0           | 0 / 0           |  |
| Ankle fracture<br>subjects affected / exposed                      | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to<br>treatment / all                 | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                      | 0 / 0           | 0 / 0           |  |
| Fall<br>subjects affected / exposed                                | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to<br>treatment / all                 | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                      | 0 / 0           | 0 / 0           |  |
| Hip fracture<br>subjects affected / exposed                        | 0 / 220 (0.00%) | 1 / 216 (0.46%) |  |
| occurrences causally related to<br>treatment / all                 | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                      | 0 / 0           | 0 / 0           |  |
| Upper limb fracture<br>subjects affected / exposed                 | 0 / 220 (0.00%) | 1 / 216 (0.46%) |  |
| occurrences causally related to<br>treatment / all                 | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Cardiac disorders                               |                 |                 |  |
| Atrial fibrillation                             |                 |                 |  |
| subjects affected / exposed                     | 3 / 220 (1.36%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial flutter                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Angina pectoris                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bradycardia                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 220 (0.00%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure acute                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac tamponade                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 220 (0.00%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myocarditis                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tachyarrhythmia                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Ischaemic stroke                                |                 |                 |  |
| subjects affected / exposed                     | 3 / 220 (1.36%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Seizure   |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Syncope   |                 |                 |  |
| subjects affected / exposed                     | 2 / 220 (0.91%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Autoimmune encephalopathy                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Autoimmune neuropathy                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Brain oedema                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 220 (0.00%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dyskinesia                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Encephalitis autoimmune                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intracranial pressure increased                 |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Leukoencephalopathy                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 220 (0.00%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Monoparesis                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 220 (0.00%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorder                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Presyncope                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Radiculopathy                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 220 (0.00%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Transient ischaemic attack                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 220 (0.00%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders            |                 |                 |  |
| Anaemia   |                 |                 |  |
| subjects affected / exposed                     | 2 / 220 (0.91%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Thrombocytopenia                                |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Eye disorders                                   |                 |                 |  |
| Chorioretinopathy                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diplopia  |                 |                 |  |
| subjects affected / exposed                     | 0 / 220 (0.00%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Visual impairment                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |
| Diarrhoea                                       |                 |                 |  |
| subjects affected / exposed                     | 9 / 220 (4.09%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 9           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vomiting  |                 |                 |  |
| subjects affected / exposed                     | 5 / 220 (2.27%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal pain upper                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 3 / 216 (1.39%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal pain                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 220 (0.91%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Colitis   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 220 (0.91%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nausea  |                 |                 |  |
| subjects affected / exposed                     | 2 / 220 (0.91%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ascites   |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Autoimmune colitis                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 220 (0.00%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastric ulcer                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 220 (0.00%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal haemorrhage                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 220 (0.00%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal obstruction                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haematochezia                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemorrhoids                                    |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intestinal obstruction                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 220 (0.00%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 220 (0.00%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rectal haemorrhage                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 220 (0.00%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Stomatitis                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Subileus  |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Thrombosis mesenteric vessel                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Hepatic failure                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 220 (0.00%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatic pain                                    |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatitis                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 220 (0.00%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |                 |                 |  |
| Rash  |                 |                 |  |
| subjects affected / exposed                     | 4 / 220 (1.82%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dermatitis acneiform                            |                 |                 |  |
| subjects affected / exposed                     | 3 / 220 (1.36%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dermatitis                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dermatitis allergic                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dermatitis exfoliative generalised              |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pemphigoid                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rash macular                                    |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Renal failure                                   |                 |                 |  |
| subjects affected / exposed                     | 3 / 220 (1.36%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute kidney injury                             |                 |                 |  |
| subjects affected / exposed                     | 2 / 220 (0.91%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bladder perforation                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 220 (0.00%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haematuria                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Endocrine disorders                             |                 |                 |  |
| Adrenal insufficiency                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 220 (0.00%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Rhabdomyolysis                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dupuytren's contracture                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Muscular weakness                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myositis  |                 |                 |  |
| subjects affected / exposed                     | 0 / 220 (0.00%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Scleroderma                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal pain                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 220 (0.00%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Sepsis  |                 |                 |  |
| subjects affected / exposed                     | 6 / 220 (2.73%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Erysipelas                                      |                 |                 |  |
| subjects affected / exposed                     | 3 / 220 (1.36%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 2 / 220 (0.91%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urosepsis                                       |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 220 (0.91%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cellulitis                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dacryocystitis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 220 (0.00%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Device related sepsis                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 220 (0.00%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diarrhoea infectious                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Encephalitis                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Endocarditis                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infection                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 220 (0.00%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Influenza                                       |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 220 (0.00%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lower respiratory tract infection               |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung infection                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory tract infection                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spleen tuberculosis                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 220 (0.00%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Superinfection viral                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 220 (0.00%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Toxic shock syndrome                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Upper respiratory tract infection               |                 |                 |  |
| subjects affected / exposed                     | 0 / 220 (0.00%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vascular device infection                       |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wound infection                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Hyperglycaemia                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dehydration                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diabetes mellitus                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 220 (0.00%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoglycaemia                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 220 (0.00%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyponatraemia                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 220 (0.45%) | 0 / 216 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypovolaemia                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 220 (0.00%) | 1 / 216 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | <b>Cobimetinib and Atezolizumab</b> | <b>Pembrolizumab</b> |  |
|---|-------------------------------------|----------------------|--|
| Total subjects affected by non-serious adverse events |                                     |                      |  |
| subjects affected / exposed                           | 209 / 220 (95.00%)                  | 162 / 216 (75.00%)   |  |
| Investigations  |                                     |                      |  |
| Alanine aminotransferase increased                    |                                     |                      |  |
| subjects affected / exposed                           | 26 / 220 (11.82%)                   | 14 / 216 (6.48%)     |  |
| occurrences (all)                                     | 36                                  | 14                   |  |
| Amylase increased                                     |                                     |                      |  |
| subjects affected / exposed                           | 14 / 220 (6.36%)                    | 7 / 216 (3.24%)      |  |
| occurrences (all)                                     | 23                                  | 8                    |  |
| Aspartate aminotransferase increased                  |                                     |                      |  |
| subjects affected / exposed                           | 38 / 220 (17.27%)                   | 14 / 216 (6.48%)     |  |
| occurrences (all)                                     | 50                                  | 14                   |  |
| Blood creatine phosphokinase increased                |                                     |                      |  |
| subjects affected / exposed                           | 76 / 220 (34.55%)                   | 9 / 216 (4.17%)      |  |
| occurrences (all)                                     | 108                                 | 12                   |  |
| Blood lactate dehydrogenase increased                 |                                     |                      |  |
| subjects affected / exposed                           | 12 / 220 (5.45%)                    | 4 / 216 (1.85%)      |  |
| occurrences (all)                                     | 14                                  | 4                    |  |
| Lipase increased                                      |                                     |                      |  |
| subjects affected / exposed                           | 22 / 220 (10.00%)                   | 12 / 216 (5.56%)     |  |
| occurrences (all)                                     | 39                                  | 14                   |  |
| Vascular disorders                                    |                                     |                      |  |
| Hypertension  |                                     |                      |  |
| subjects affected / exposed                           | 21 / 220 (9.55%)                    | 11 / 216 (5.09%)     |  |
| occurrences (all)                                     | 26                                  | 15                   |  |
| Nervous system disorders                              |                                     |                      |  |
| Dizziness   |                                     |                      |  |
| subjects affected / exposed                           | 14 / 220 (6.36%)                    | 7 / 216 (3.24%)      |  |
| occurrences (all)                                     | 18                                  | 10                   |  |
| Headache  |                                     |                      |  |
| subjects affected / exposed                           | 24 / 220 (10.91%)                   | 17 / 216 (7.87%)     |  |
| occurrences (all)                                     | 30                                  | 18                   |  |

|  |                    |                   |  |
|--|--------------------|-------------------|--|
| Blood and lymphatic system disorders                 |                    |                   |  |
| Anaemia  |                    |                   |  |
| subjects affected / exposed                          | 30 / 220 (13.64%)  | 12 / 216 (5.56%)  |  |
| occurrences (all)                                    | 41                 | 12                |  |
| General disorders and administration site conditions |                    |                   |  |
| Asthenia   |                    |                   |  |
| subjects affected / exposed                          | 55 / 220 (25.00%)  | 39 / 216 (18.06%) |  |
| occurrences (all)                                    | 76                 | 43                |  |
| Fatigue  |                    |                   |  |
| subjects affected / exposed                          | 42 / 220 (19.09%)  | 41 / 216 (18.98%) |  |
| occurrences (all)                                    | 61                 | 53                |  |
| Oedema peripheral                                    |                    |                   |  |
| subjects affected / exposed                          | 45 / 220 (20.45%)  | 13 / 216 (6.02%)  |  |
| occurrences (all)                                    | 63                 | 13                |  |
| Pyrexia  |                    |                   |  |
| subjects affected / exposed                          | 62 / 220 (28.18%)  | 15 / 216 (6.94%)  |  |
| occurrences (all)                                    | 82                 | 16                |  |
| Gastrointestinal disorders                           |                    |                   |  |
| Abdominal pain                                       |                    |                   |  |
| subjects affected / exposed                          | 22 / 220 (10.00%)  | 13 / 216 (6.02%)  |  |
| occurrences (all)                                    | 26                 | 16                |  |
| Constipation   |                    |                   |  |
| subjects affected / exposed                          | 30 / 220 (13.64%)  | 18 / 216 (8.33%)  |  |
| occurrences (all)                                    | 33                 | 21                |  |
| Diarrhoea  |                    |                   |  |
| subjects affected / exposed                          | 118 / 220 (53.64%) | 35 / 216 (16.20%) |  |
| occurrences (all)                                    | 246                | 44                |  |
| Dry mouth  |                    |                   |  |
| subjects affected / exposed                          | 16 / 220 (7.27%)   | 6 / 216 (2.78%)   |  |
| occurrences (all)                                    | 17                 | 6                 |  |
| Nausea   |                    |                   |  |
| subjects affected / exposed                          | 53 / 220 (24.09%)  | 26 / 216 (12.04%) |  |
| occurrences (all)                                    | 59                 | 30                |  |
| Stomatitis   |                    |                   |  |
| subjects affected / exposed                          | 12 / 220 (5.45%)   | 3 / 216 (1.39%)   |  |
| occurrences (all)                                    | 16                 | 4                 |  |

|   |   |  |  |
|---|---|--|--|
| Vomiting<br>subjects affected / exposed<br>occurrences (all)  | 39 / 220 (17.73%)<br>49   | 15 / 216 (6.94%)<br>15   |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)<br><br>Dyspnoea<br>subjects affected / exposed<br>occurrences (all)  | <br>17 / 220 (7.73%)<br>20<br><br>15 / 220 (6.82%)<br>21  | <br>18 / 216 (8.33%)<br>20<br><br>16 / 216 (7.41%)<br>16   |  |
| Skin and subcutaneous tissue disorders<br>Dermatitis acneiform<br>subjects affected / exposed<br>occurrences (all)<br><br>Dry skin<br>subjects affected / exposed<br>occurrences (all)<br><br>Erythema<br>subjects affected / exposed<br>occurrences (all)<br><br>Pruritis<br>subjects affected / exposed<br>occurrences (all)<br><br>Rash<br>subjects affected / exposed<br>occurrences (all)<br><br>Rash maculo-papular<br>subjects affected / exposed<br>occurrences (all) | <br>50 / 220 (22.73%)<br>62<br><br>14 / 220 (6.36%)<br>17<br><br>12 / 220 (5.45%)<br>13<br><br>39 / 220 (17.73%)<br>48<br><br>89 / 220 (40.45%)<br>132<br><br>26 / 220 (11.82%)<br>36 | <br>3 / 216 (1.39%)<br>3<br><br>11 / 216 (5.09%)<br>12<br><br>6 / 216 (2.78%)<br>6<br><br>30 / 216 (13.89%)<br>37<br><br>25 / 216 (11.57%)<br>34<br><br>5 / 216 (2.31%)<br>6 |  |
| Endocrine disorders<br>Hyperthyroidism<br>subjects affected / exposed<br>occurrences (all)<br><br>Hypothyroidism<br>subjects affected / exposed<br>occurrences (all)  | <br>7 / 220 (3.18%)<br>7<br><br>13 / 220 (5.91%)<br>14  | <br>19 / 216 (8.80%)<br>19<br><br>15 / 216 (6.94%)<br>15   |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| Musculoskeletal and connective tissue disorders |                   |                   |  |
| Arthralgia                                      |                   |                   |  |
| subjects affected / exposed                     | 14 / 220 (6.36%)  | 24 / 216 (11.11%) |  |
| occurrences (all)                               | 15                | 30                |  |
| Back pain                                       |                   |                   |  |
| subjects affected / exposed                     | 12 / 220 (5.45%)  | 19 / 216 (8.80%)  |  |
| occurrences (all)                               | 15                | 19                |  |
| Myalgia   |                   |                   |  |
| subjects affected / exposed                     | 13 / 220 (5.91%)  | 10 / 216 (4.63%)  |  |
| occurrences (all)                               | 15                | 10                |  |
| Pain in extremity                               |                   |                   |  |
| subjects affected / exposed                     | 11 / 220 (5.00%)  | 7 / 216 (3.24%)   |  |
| occurrences (all)                               | 11                | 8                 |  |
| Infections and infestations                     |                   |                   |  |
| Folliculitis                                    |                   |                   |  |
| subjects affected / exposed                     | 13 / 220 (5.91%)  | 1 / 216 (0.46%)   |  |
| occurrences (all)                               | 20                | 1                 |  |
| Rash pustular                                   |                   |                   |  |
| subjects affected / exposed                     | 12 / 220 (5.45%)  | 1 / 216 (0.46%)   |  |
| occurrences (all)                               | 12                | 1                 |  |
| Urinary tract infection                         |                   |                   |  |
| subjects affected / exposed                     | 12 / 220 (5.45%)  | 2 / 216 (0.93%)   |  |
| occurrences (all)                               | 14                | 2                 |  |
| Metabolism and nutrition disorders              |                   |                   |  |
| Decreased appetite                              |                   |                   |  |
| subjects affected / exposed                     | 30 / 220 (13.64%) | 16 / 216 (7.41%)  |  |
| occurrences (all)                               | 33                | 18                |  |
| Hyperglycaemia                                  |                   |                   |  |
| subjects affected / exposed                     | 16 / 220 (7.27%)  | 9 / 216 (4.17%)   |  |
| occurrences (all)                               | 20                | 11                |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment  |
|-------------------|--|
| 08 August 2017    | Updated eligibility criteria; changed pembrolizumab dosing per United Surgical Partners International (USPI) |
| 12 March 2018     | Added IRB assessment for secondary endpoints ORR and DOR; updated eligibility criteria                       |
| 19 September 2018 | Updated eligibility criteria   |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported