



## Clinical trial results:

### A Multicenter, Randomized, Open-label Study in Patients with esophageal Cancer refractory or intolerant to Combination Therapy with Fluoropyrimidine and Platinum-based Drugs

#### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2015-003339-36  |
| Trial protocol           | DE DK GB IT     |
| Global end of trial date | 23 October 2020 |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 06 December 2024 |
| First version publication date | 06 December 2024 |

#### Trial information

##### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | CA209-473 |
|-----------------------|-----------|

##### Additional study identifiers

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

Notes:

#### Sponsors

|                              |                                                                                                 |
|------------------------------|-------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Bristol-Myers Squibb                                                                            |
| Sponsor organisation address | Chaussee de la Hulpe 185, Brussels, Belgium, 1170                                               |
| Public contact               | EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com |
| Scientific contact           | Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.com              |

Notes:

#### Paediatric regulatory details

|                                                                      |    |
|----------------------------------------------------------------------|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|                                                      |                 |
|------------------------------------------------------|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 23 October 2020 |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 23 October 2020 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

To compare overall survival (OS) between the nivolumab group and control group (docetaxel or paclitaxel) in patients with esophageal cancer refractory or intolerant to combination therapy with fluoropyrimidine- and platinum-based drugs.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial participants were followed.

Background therapy: -

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 14 December 2015 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                                            |
|--------------------------------------|--------------------------------------------|
| Country: Number of subjects enrolled | Japan: 274                                 |
| Country: Number of subjects enrolled | Korea, Democratic People's Republic of: 59 |
| Country: Number of subjects enrolled | Taiwan: 68                                 |
| Country: Number of subjects enrolled | United States: 1                           |
| Country: Number of subjects enrolled | Germany: 7                                 |
| Country: Number of subjects enrolled | Italy: 6                                   |
| Country: Number of subjects enrolled | Denmark: 4                                 |
| Worldwide total number of subjects   | 419                                        |
| EEA total number of subjects         | 17                                         |

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)      | 197 |
| From 65 to 84 years       | 221 |
| 85 years and over         | 1   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

419 participants were randomized, 417 were treated

### Period 1

|                              |                         |
|------------------------------|-------------------------|
| Period 1 title               | Pre-Treatment 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>             | Nivolumab Arm |

Arm description:

Nivolumab 240 mg/body solution intravenously every 2 weeks until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends

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

Dosage and administration details:

240 mg at 2-week intervals

|                  |                                            |
|------------------|--------------------------------------------|
| <b>Arm title</b> | Active Comparator Arm Docetaxel/Paclitaxel |
|------------------|--------------------------------------------|

Arm description:

Docetaxel: Intravenously administered at a dose of 75 mg/m<sup>2</sup> every 3 weeks until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends OR Paclitaxel: Intravenously administered at a dose of 100 mg/m<sup>2</sup> weekly for 6 weeks followed by 2-week drug holiday until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends

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

Dosage and administration details:

100 mg/m<sup>2</sup> weekly for 6 weeks in succession followed by a 2-week drug holiday

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

Dosage and administration details:

75 mg/m<sup>2</sup> at 3-week intervals

| Number of subjects in period 1 | Nivolumab Arm | Active Comparator Arm<br>Docetaxel/Paclitaxel |
|--------------------------------|---------------|-----------------------------------------------|
|                                |               |                                               |
| Started                        | 210           | 209                                           |
| Completed                      | 209           | 208                                           |
| Not completed                  | 1             | 1                                             |
| Adverse event, serious fatal   | 1             | -                                             |
| Consent withdrawn by subject   | -             | 1                                             |

## Period 2

|                              |                         |
|------------------------------|-------------------------|
| Period 2 title               | Treatment Period        |
| Is this the baseline period? | No                      |
| Allocation method            | Randomised - controlled |
| Blinding used                | Not blinded             |

## Arms

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

Arm description:

Nivolumab 240 mg/body solution intravenously every 2 weeks until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends

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

Dosage and administration details:

240 mg at 2-week intervals

|                  |                                            |
|------------------|--------------------------------------------|
| <b>Arm title</b> | Active Comparator Arm Docetaxel/Paclitaxel |
|------------------|--------------------------------------------|

Arm description:

Docetaxel: Intravenously administered at a dose of 75 mg/m<sup>2</sup> every 3 weeks until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends OR Paclitaxel: Intravenously administered at a dose of 100 mg/m<sup>2</sup> weekly for 6 weeks followed by 2-week drug holiday until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends

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

Dosage and administration details:

100 mg/m<sup>2</sup> weekly for 6 weeks in succession followed by a 2-week drug holiday

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

Dosage and administration details:

75 mg/m<sup>2</sup> at 3-week intervals

| Number of subjects in period 2 | Nivolumab Arm | Active Comparator Arm<br>Docetaxel/Paclitaxel |
|--------------------------------|---------------|-----------------------------------------------|
|                                |               |                                               |
| Started                        | 209           | 208                                           |
| Completed                      | 0             | 0                                             |
| Not completed                  | 209           | 208                                           |
| Other reasons                  | 209           | 208                                           |

## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                            |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                       | Nivolumab Arm                              |
| Reporting group description:<br>Nivolumab 240 mg/body solution intravenously every 2 weeks until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends                                                                                                                                                                                                                                                   |                                            |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                       | Active Comparator Arm Docetaxel/Paclitaxel |
| Reporting group description:<br>Docetaxel: Intravenously administered at a dose of 75 mg/m2 every 3 weeks until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends OR Paclitaxel: Intravenously administered at a dose of 100 mg/m2 weekly for 6 weeks followed by 2-week drug holiday until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends |                                            |

| Reporting group values                    | Nivolumab Arm | Active Comparator Arm<br>Docetaxel/Paclitaxel | Total |
|-------------------------------------------|---------------|-----------------------------------------------|-------|
| Number of subjects                        | 210           | 209                                           | 419   |
| Age Categorical<br>Units: participants    |               |                                               |       |
| <=18 years                                | 0             | 0                                             | 0     |
| Between 18 and 65 years                   | 112           | 85                                            | 197   |
| >=65 years                                | 98            | 124                                           | 222   |
| Age Continuous<br>Units: years            |               |                                               |       |
| arithmetic mean                           | 64            | 67                                            |       |
| inter-quartile range (Q1-Q3)              | 57 to 69      | 57 to 72                                      | -     |
| Sex: Female, Male<br>Units: participants  |               |                                               |       |
| Female                                    | 31            | 24                                            | 55    |
| Male                                      | 179           | 185                                           | 364   |
| Race (NIH/OMB)<br>Units: Subjects         |               |                                               |       |
| American Indian or Alaska Native          | 0             | 0                                             | 0     |
| Asian                                     | 201           | 200                                           | 401   |
| Native Hawaiian or Other Pacific Islander | 0             | 0                                             | 0     |
| Black or African American                 | 0             | 0                                             | 0     |
| White                                     | 9             | 9                                             | 18    |
| More than one race                        | 0             | 0                                             | 0     |
| Unknown or Not Reported                   | 0             | 0                                             | 0     |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                            |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Nivolumab Arm                              |
| Reporting group description:<br>Nivolumab 240 mg/body solution intravenously every 2 weeks until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends                                                                                                                                                                                                                                                                           |                                            |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Active Comparator Arm Docetaxel/Paclitaxel |
| Reporting group description:<br>Docetaxel: Intravenously administered at a dose of 75 mg/m <sup>2</sup> every 3 weeks until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends OR Paclitaxel: Intravenously administered at a dose of 100 mg/m <sup>2</sup> weekly for 6 weeks followed by 2-week drug holiday until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends |                                            |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Nivolumab Arm                              |
| Reporting group description:<br>Nivolumab 240 mg/body solution intravenously every 2 weeks until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends                                                                                                                                                                                                                                                                           |                                            |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Active Comparator Arm Docetaxel/Paclitaxel |
| Reporting group description:<br>Docetaxel: Intravenously administered at a dose of 75 mg/m <sup>2</sup> every 3 weeks until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends OR Paclitaxel: Intravenously administered at a dose of 100 mg/m <sup>2</sup> weekly for 6 weeks followed by 2-week drug holiday until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends |                                            |

### Primary: Overall Survival (OS)

|                                                                                                                                                                                                                                                                                                                                               |                       |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| End point title                                                                                                                                                                                                                                                                                                                               | Overall Survival (OS) |
| End point description:<br>Overall survival (OS) is defined as the time from randomization to death from any cause. For participants lost to follow-up and participants who were alive at the time of data cutoff date, data was censored at the time the participant was last confirmed to be alive. Conducted using the Kaplan-Meier method. |                       |
| End point type                                                                                                                                                                                                                                                                                                                                | Primary               |
| End point timeframe:<br>From date of randomization until the date of death due to any cause (assessed up to approximately 58 months)                                                                                                                                                                                                          |                       |

| End point values                 | Nivolumab Arm         | Active Comparator Arm Docetaxel/Paclitaxel |  |  |
|----------------------------------|-----------------------|--------------------------------------------|--|--|
| Subject group type               | Reporting group       | Reporting group                            |  |  |
| Number of subjects analysed      | 210                   | 209                                        |  |  |
| Units: Months                    |                       |                                            |  |  |
| median (confidence interval 95%) | 10.91 (9.23 to 13.34) | 8.51 (7.29 to 9.86)                        |  |  |

## Statistical analyses

|                                         |                                                            |
|-----------------------------------------|------------------------------------------------------------|
| <b>Statistical analysis title</b>       | Hazard Ratio                                               |
| Comparison groups                       | Nivolumab Arm v Active Comparator Arm Docetaxel/Paclitaxel |
| Number of subjects included in analysis | 419                                                        |
| Analysis specification                  | Pre-specified                                              |
| Analysis type                           |                                                            |
| P-value                                 | = 0.0189                                                   |
| Method                                  | Regression, Cox                                            |
| Parameter estimate                      | Hazard ratio (HR)                                          |
| Point estimate                          | 0.79                                                       |
| Confidence interval                     |                                                            |
| level                                   | 95 %                                                       |
| sides                                   | 2-sided                                                    |
| lower limit                             | 0.64                                                       |
| upper limit                             | 0.97                                                       |

## Secondary: Progression-Free Survival (PFS)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                 |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Progression-Free Survival (PFS) |
| End point description:<br>Progression-free survival (PFS) is the time from randomization until disease progression or worsening. Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Conducted by using the Kaplan-Meier method |                                 |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Secondary                       |
| End point timeframe:<br>From date of randomization until progressive disease or death due to any cause (assessed up to approximately 58 months)                                                                                                                                                                                                                                                                                                                                                             |                                 |

|                                  |                     |                                               |  |  |
|----------------------------------|---------------------|-----------------------------------------------|--|--|
| <b>End point values</b>          | Nivolumab Arm       | Active Comparator Arm<br>Docetaxel/Paclitaxel |  |  |
| Subject group type               | Reporting group     | Reporting group                               |  |  |
| Number of subjects analysed      | 210                 | 209                                           |  |  |
| Units: Months                    |                     |                                               |  |  |
| median (confidence interval 95%) | 1.68 (1.51 to 2.73) | 3.35 (2.99 to 4.21)                           |  |  |

## Statistical analyses

|                                         |                                                            |
|-----------------------------------------|------------------------------------------------------------|
| <b>Statistical analysis title</b>       | Hazard Ratio (HR)                                          |
| Comparison groups                       | Nivolumab Arm v Active Comparator Arm Docetaxel/Paclitaxel |
| Number of subjects included in analysis | 419                                                        |
| Analysis specification                  | Pre-specified                                              |
| Analysis type                           |                                                            |
| Method                                  | Regression, Cox                                            |
| Parameter estimate                      | Hazard ratio (HR)                                          |
| Point estimate                          | 1.07                                                       |
| Confidence interval                     |                                                            |
| level                                   | 95 %                                                       |
| sides                                   | 2-sided                                                    |
| lower limit                             | 0.87                                                       |
| upper limit                             | 1.33                                                       |

## Secondary: Duration of Response (DoR)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                            |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Duration of Response (DoR) |
| End point description:<br>Duration of response (DoR) measures the length of time that a tumor responds to treatment without growing or spreading i.e. the length of time a participant had either a complete response (CR) or partial response (PR) to study treatment.<br>Complete Response (CR): Disappearance of all (non-lymph node) target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in the short axis to <10 mm.<br>Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Conducted by using the Kaplan-Meier method. |                            |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Secondary                  |
| End point timeframe:<br>From randomization until progression or death due to any cause (assessed up to approximately 58 months)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                            |

| End point values                 | Nivolumab Arm        | Active Comparator Arm<br>Docetaxel/Paclitaxel |  |  |
|----------------------------------|----------------------|-----------------------------------------------|--|--|
| Subject group type               | Reporting group      | Reporting group                               |  |  |
| Number of subjects analysed      | 171                  | 158                                           |  |  |
| Units: Months                    |                      |                                               |  |  |
| median (confidence interval 95%) | 6.93 (5.39 to 11.14) | 3.91 (2.79 to 4.17)                           |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Objective Response Rate (ORR)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                               |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Objective Response Rate (ORR) |
| End point description:<br>Objective response rate (ORR) is defined as the percentage of participants whose best overall response is assessed as either complete response (CR) or partial response (PR). Overall response and best overall response was determined solely by imaging assessment according to the RECIST Guideline Version 1.1 and did not take into account any clinical/symptomatic progression.<br>Complete Response (CR): Disappearance of all (non-lymph node) target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in the short axis to <10 mm.<br>Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. |                               |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Secondary                     |
| End point timeframe:<br>From randomization until progressive disease or death due to any cause (assessed up to approximately 58 months)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                               |

| End point values                 | Nivolumab Arm       | Active Comparator Arm<br>Docetaxel/Paclitaxel |  |  |
|----------------------------------|---------------------|-----------------------------------------------|--|--|
| Subject group type               | Reporting group     | Reporting group                               |  |  |
| Number of subjects analysed      | 210                 | 209                                           |  |  |
| Units: Percent of Participants   |                     |                                               |  |  |
| number (confidence interval 95%) | 15.7 (11.1 to 21.4) | 16.3 (11.5 to 22.0)                           |  |  |

## Statistical analyses

|                            |                                                            |
|----------------------------|------------------------------------------------------------|
| Statistical analysis title | Odds Ratio (OR)                                            |
| Comparison groups          | Nivolumab Arm v Active Comparator Arm Docetaxel/Paclitaxel |

|                                         |                 |
|-----------------------------------------|-----------------|
| Number of subjects included in analysis | 419             |
| Analysis specification                  | Pre-specified   |
| Analysis type                           |                 |
| Method                                  | Mantel-Haenszel |
| Parameter estimate                      | Odds ratio (OR) |
| Point estimate                          | 0.96            |
| Confidence interval                     |                 |
| level                                   | 95 %            |
| sides                                   | 2-sided         |
| lower limit                             | 0.57            |
| upper limit                             | 1.62            |

## Secondary: Disease Control Rate (DCR)

|                                                                                                                                                                                            |                            |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|
| End point title                                                                                                                                                                            | Disease Control Rate (DCR) |
| End point description:                                                                                                                                                                     |                            |
| Disease control rate is defined as the percentage of participants whose best overall response is assessed as complete response (CR), partial response (PR) or stable disease (SD).         |                            |
| Complete Response (CR): Disappearance of all (non-lymph node) target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in the short axis to <10 mm. |                            |
| Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.                                                  |                            |
| Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameter while on study.               |                            |
| End point type                                                                                                                                                                             | Secondary                  |
| End point timeframe:                                                                                                                                                                       |                            |
| From randomization until progressive disease or death due to any cause (assessed up to approximately 58 months)                                                                            |                            |

| End point values                 | Nivolumab Arm       | Active Comparator Arm<br>Docetaxel/Paclitaxel |  |  |
|----------------------------------|---------------------|-----------------------------------------------|--|--|
| Subject group type               | Reporting group     | Reporting group                               |  |  |
| Number of subjects analysed      | 210                 | 209                                           |  |  |
| Units: Percent of participants   |                     |                                               |  |  |
| number (confidence interval 95%) | 30.5 (24.3 to 37.2) | 47.4 (40.4 to 54.4)                           |  |  |

## Statistical analyses

|                            |                                                            |
|----------------------------|------------------------------------------------------------|
| Statistical analysis title | Odds Ratio (OR)                                            |
| Comparison groups          | Nivolumab Arm v Active Comparator Arm Docetaxel/Paclitaxel |

|                                         |                 |
|-----------------------------------------|-----------------|
| Number of subjects included in analysis | 419             |
| Analysis specification                  | Pre-specified   |
| Analysis type                           |                 |
| Method                                  | Mantel-Haenszel |
| Parameter estimate                      | Odds ratio (OR) |
| Point estimate                          | 0.48            |
| Confidence interval                     |                 |
| level                                   | 95 %            |
| sides                                   | 2-sided         |
| lower limit                             | 0.32            |
| upper limit                             | 0.72            |

## Secondary: Time to Response (TTR)

|                                                                                                                                                                                            |                        |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| End point title                                                                                                                                                                            | Time to Response (TTR) |
| End point description:                                                                                                                                                                     |                        |
| Time to response (TTR) is the duration from the start of treatment to the first observation of a predefined clinical response.                                                             |                        |
| Complete Response (CR): Disappearance of all (non-lymph node) target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in the short axis to <10 mm. |                        |
| Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.                                                  |                        |
| End point type                                                                                                                                                                             | Secondary              |
| End point timeframe:                                                                                                                                                                       |                        |
| From randomization until complete response or partial response (assessed up to approximately 58 months)                                                                                    |                        |

| End point values                       | Nivolumab Arm      | Active Comparator Arm<br>Docetaxel/Paclitaxel |  |  |
|----------------------------------------|--------------------|-----------------------------------------------|--|--|
| Subject group type                     | Reporting group    | Reporting group                               |  |  |
| Number of subjects analysed            | 210                | 209                                           |  |  |
| Units: Months                          |                    |                                               |  |  |
| arithmetic mean (full range (min-max)) | 2.66 (1.2 to 22.3) | 1.48 (1.2 to 5.6)                             |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Best Overall Response (BOR)

|                                                                                                                                                                                            |                             |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| End point title                                                                                                                                                                            | Best Overall Response (BOR) |
| End point description:                                                                                                                                                                     |                             |
| Best overall response (BOR) refers to the best response recorded from the start of the treatment until disease progression or recurrence.                                                  |                             |
| Complete Response (CR): Disappearance of all (non-lymph node) target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in the short axis to <10 mm. |                             |

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

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

End point timeframe:

From randomization until progressive disease or death due to any cause (assessed up to approximately 58 months)

| End point values               | Nivolumab Arm   | Active Comparator Arm<br>Docetaxel/Paclitaxel |  |  |
|--------------------------------|-----------------|-----------------------------------------------|--|--|
| Subject group type             | Reporting group | Reporting group                               |  |  |
| Number of subjects analysed    | 210             | 209                                           |  |  |
| Units: Percent of participants |                 |                                               |  |  |
| number (not applicable)        |                 |                                               |  |  |
| Complete Response (CR)         | 1.0             | 1.0                                           |  |  |
| Partial Response (PR)          | 14.8            | 15.3                                          |  |  |
| Progressive Disease (PD)       | 44.3            | 24.4                                          |  |  |
| Stable Disease (SD)            | 14.8            | 31.1                                          |  |  |
| Not Evaluable (NE)             | 25.2            | 28.2                                          |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Best Percent Reduction from Baseline in the Sum of Diameters of the Target Lesion

|                 |                                                                                   |
|-----------------|-----------------------------------------------------------------------------------|
| End point title | Best Percent Reduction from Baseline in the Sum of Diameters of the Target Lesion |
|-----------------|-----------------------------------------------------------------------------------|

End point description:

Best percent reduction from baseline in the sum of diameters of the target lesion was used to evaluate the effectiveness of treatment in reducing tumor size. The diameter data excludes that obtained after an overall response of progressive disease (PD) and after new treatment for cancer.

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

End point timeframe:

From randomization until progressive disease or death due to any cause (assessed up to approximately 58 months)

| <b>End point values</b>                | Nivolumab Arm   | Active<br>Comparator<br>Arm<br>Docetaxel/Paclitaxel |  |  |
|----------------------------------------|-----------------|-----------------------------------------------------|--|--|
| Subject group type                     | Reporting group | Reporting group                                     |  |  |
| Number of subjects analysed            | 210             | 209                                                 |  |  |
| Units: Percent reduction from baseline | 100             | 100                                                 |  |  |

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Monitoring for non-serious adverse events (AEs) continued until 28 days after the treatment phase ended. Serious AEs were tracked during the treatment period and for 100 days after the last dose.

Adverse event reporting additional description:

Serious AEs and non-serious AEs included participants who received at least one dose of study medicine.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 21.1 |
|--------------------|------|

### Reporting groups

|                       |                                            |
|-----------------------|--------------------------------------------|
| Reporting group title | Active Comparator Arm Docetaxel/Paclitaxel |
|-----------------------|--------------------------------------------|

Reporting group description:

Docetaxel: Intravenously administered at a dose of 75 mg/m<sup>2</sup> every 3 weeks until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends OR Paclitaxel: Intravenously administered at a dose of 100 mg/m<sup>2</sup> weekly for 6 weeks followed by 2-week drug holiday until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends.

|                       |               |
|-----------------------|---------------|
| Reporting group title | Nivolumab Arm |
|-----------------------|---------------|

Reporting group description:

Nivolumab 240 mg/body solution intravenously every 2 weeks until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends.

| Serious adverse events                                              | Active Comparator Arm<br>Docetaxel/Paclitaxel | Nivolumab Arm     |  |
|---------------------------------------------------------------------|-----------------------------------------------|-------------------|--|
| Total subjects affected by serious adverse events                   |                                               |                   |  |
| subjects affected / exposed                                         | 78 / 208 (37.50%)                             | 70 / 209 (33.49%) |  |
| number of deaths (all causes)                                       | 186                                           | 178               |  |
| number of deaths resulting from adverse events                      |                                               |                   |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                               |                   |  |
| Metastases to lymph nodes                                           |                                               |                   |  |
| subjects affected / exposed                                         | 0 / 208 (0.00%)                               | 1 / 209 (0.48%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0                                         | 0 / 1             |  |
| deaths causally related to treatment / all                          | 0 / 0                                         | 0 / 1             |  |
| Cancer pain                                                         |                                               |                   |  |
| subjects affected / exposed                                         | 0 / 208 (0.00%)                               | 1 / 209 (0.48%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0                                         | 0 / 1             |  |
| deaths causally related to treatment / all                          | 0 / 0                                         | 0 / 0             |  |
| Lymphangiosis carcinomatosa                                         |                                               |                   |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 208 (0.00%) | 1 / 209 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Malignant neoplasm progression                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 208 (0.00%) | 2 / 209 (0.96%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Tumour haemorrhage                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 208 (0.48%) | 3 / 209 (1.44%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 3 / 3           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Skin cancer                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 208 (0.48%) | 0 / 209 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vascular disorders                              |                 |                 |  |
| Embolism                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 208 (0.48%) | 0 / 209 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Venous thrombosis                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 208 (0.48%) | 0 / 209 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypotension                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 208 (0.48%) | 0 / 209 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Surgical and medical procedures                 |                 |                 |  |
| Jejunostomy                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 208 (0.00%) | 1 / 209 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| General disorders and administration            |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| site conditions                                 |                 |                 |  |
| Asthenia                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 208 (0.48%) | 0 / 209 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Fatigue                                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 208 (0.48%) | 1 / 209 (0.48%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Malaise                                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 208 (0.48%) | 1 / 209 (0.48%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pyrexia                                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 208 (0.48%) | 6 / 209 (2.87%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 6 / 7           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sudden death                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 208 (0.48%) | 1 / 209 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| Disease progression                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 208 (0.48%) | 0 / 209 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Stenosis                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 208 (0.48%) | 0 / 209 (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                         |                 |                 |  |
| Drug hypersensitivity                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 208 (0.00%) | 1 / 209 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Anaphylactic shock                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 208 (0.00%) | 1 / 209 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Respiratory failure                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 208 (0.00%) | 1 / 209 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Pulmonary embolism                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 208 (0.00%) | 1 / 209 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Pneumothorax spontaneous                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 208 (0.00%) | 1 / 209 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumothorax                                    |                 |                 |  |
| subjects affected / exposed                     | 3 / 208 (1.44%) | 1 / 209 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonitis                                     |                 |                 |  |
| subjects affected / exposed                     | 3 / 208 (1.44%) | 3 / 209 (1.44%) |  |
| occurrences causally related to treatment / all | 2 / 3           | 2 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 2           |  |
| Pneumonia aspiration                            |                 |                 |  |
| subjects affected / exposed                     | 2 / 208 (0.96%) | 3 / 209 (1.44%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 7           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pleurisy                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 208 (0.48%) | 0 / 209 (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                     | 3 / 208 (1.44%) | 1 / 209 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Interstitial lung disease                       |                 |                 |  |
| subjects affected / exposed                     | 3 / 208 (1.44%) | 4 / 209 (1.91%) |  |
| occurrences causally related to treatment / all | 3 / 3           | 4 / 4           |  |
| deaths causally related to treatment / all      | 1 / 1           | 1 / 1           |  |
| Dyspnoea                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 208 (0.48%) | 4 / 209 (1.91%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tracheal fistula                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 208 (0.00%) | 1 / 209 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oesophagobronchial fistula                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 208 (0.00%) | 2 / 209 (0.96%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Investigations                                  |                 |                 |  |
| Blood creatine phosphokinase increased          |                 |                 |  |
| subjects affected / exposed                     | 0 / 208 (0.00%) | 1 / 209 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood creatinine increased                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 208 (0.00%) | 1 / 209 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neutrophil count decreased                      |                 |                 |  |
| subjects affected / exposed                     | 3 / 208 (1.44%) | 0 / 209 (0.00%) |  |
| occurrences causally related to treatment / all | 4 / 4           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                              |                 |                 |  |
|--------------------------------------------------------------|-----------------|-----------------|--|
| Liver function test increased<br>subjects affected / exposed | 0 / 208 (0.00%) | 1 / 209 (0.48%) |  |
| 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            |                 |                 |  |
| Radiation pneumonitis<br>subjects affected / exposed         | 0 / 208 (0.00%) | 1 / 209 (0.48%) |  |
| occurrences causally related to<br>treatment / all           | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                | 0 / 0           | 0 / 0           |  |
| Stoma site extravasation<br>subjects affected / exposed      | 1 / 208 (0.48%) | 0 / 209 (0.00%) |  |
| occurrences causally related to<br>treatment / all           | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                | 0 / 0           | 0 / 0           |  |
| Congenital, familial and genetic<br>disorders                |                 |                 |  |
| Tracheo-oesophageal fistula<br>subjects affected / exposed   | 0 / 208 (0.00%) | 1 / 209 (0.48%) |  |
| occurrences causally related to<br>treatment / all           | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                                            |                 |                 |  |
| Pericarditis<br>subjects affected / exposed                  | 1 / 208 (0.48%) | 0 / 209 (0.00%) |  |
| occurrences causally related to<br>treatment / all           | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                | 0 / 0           | 0 / 0           |  |
| Cardiac failure<br>subjects affected / exposed               | 1 / 208 (0.48%) | 0 / 209 (0.00%) |  |
| occurrences causally related to<br>treatment / all           | 1 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                | 0 / 0           | 0 / 0           |  |
| Angina pectoris<br>subjects affected / exposed               | 0 / 208 (0.00%) | 1 / 209 (0.48%) |  |
| occurrences causally related to<br>treatment / all           | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders                         |                 |                 |  |
| Bone marrow failure                                          |                 |                 |  |

|                                                 |                  |                 |  |
|-------------------------------------------------|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 208 (0.48%)  | 0 / 209 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pancytopenia                                    |                  |                 |  |
| subjects affected / exposed                     | 1 / 208 (0.48%)  | 0 / 209 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Febrile neutropenia                             |                  |                 |  |
| subjects affected / exposed                     | 16 / 208 (7.69%) | 0 / 209 (0.00%) |  |
| occurrences causally related to treatment / all | 23 / 23          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Anaemia                                         |                  |                 |  |
| subjects affected / exposed                     | 0 / 208 (0.00%)  | 2 / 209 (0.96%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Gastrointestinal disorders                      |                  |                 |  |
| Colitis                                         |                  |                 |  |
| subjects affected / exposed                     | 0 / 208 (0.00%)  | 1 / 209 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Diarrhoea                                       |                  |                 |  |
| subjects affected / exposed                     | 2 / 208 (0.96%)  | 1 / 209 (0.48%) |  |
| occurrences causally related to treatment / all | 2 / 2            | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Duodenitis                                      |                  |                 |  |
| subjects affected / exposed                     | 0 / 208 (0.00%)  | 1 / 209 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Dysphagia                                       |                  |                 |  |
| subjects affected / exposed                     | 2 / 208 (0.96%)  | 2 / 209 (0.96%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Gastrointestinal haemorrhage                    |                  |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 208 (0.00%) | 1 / 209 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Ileus                                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 208 (0.48%) | 1 / 209 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal pain                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 208 (0.96%) | 1 / 209 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intestinal obstruction                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 208 (0.48%) | 1 / 209 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vomiting                                        |                 |                 |  |
| subjects affected / exposed                     | 2 / 208 (0.96%) | 0 / 209 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Upper gastrointestinal haemorrhage              |                 |                 |  |
| subjects affected / exposed                     | 1 / 208 (0.48%) | 0 / 209 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nausea                                          |                 |                 |  |
| subjects affected / exposed                     | 2 / 208 (0.96%) | 0 / 209 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastric fistula                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 208 (0.00%) | 1 / 209 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Aorto-oesophageal fistula                       |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 208 (0.00%) | 1 / 209 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Cholecystitis                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 208 (0.00%) | 1 / 209 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatic function abnormal                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 208 (0.00%) | 1 / 209 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bile duct obstruction                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 208 (0.00%) | 1 / 209 (0.48%) |  |
| 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          |                 |                 |  |
| Excessive granulation tissue                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 208 (0.48%) | 0 / 209 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Stevens-Johnson syndrome                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 208 (0.00%) | 1 / 209 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin ulcer                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 208 (0.48%) | 0 / 209 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Acute kidney injury                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 208 (0.00%) | 1 / 209 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Endocrine disorders                             |                 |                 |  |
| Adrenocorticotrophic hormone deficiency         |                 |                 |  |
| subjects affected / exposed                     | 0 / 208 (0.00%) | 1 / 209 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Inappropriate antidiuretic hormone secretion    |                 |                 |  |
| subjects affected / exposed                     | 0 / 208 (0.00%) | 1 / 209 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypopituitarism                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 208 (0.00%) | 1 / 209 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperthyroidism                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 208 (0.00%) | 1 / 209 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Fistula                                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 208 (0.48%) | 0 / 209 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Bacteraemia                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 208 (0.00%) | 2 / 209 (0.96%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Appendicitis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 208 (0.00%) | 1 / 209 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchitis                                      |                 |                 |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 208 (0.00%)  | 1 / 209 (0.48%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infection                                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 208 (0.96%)  | 1 / 209 (0.48%)  |  |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mediastinitis                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 208 (0.00%)  | 1 / 209 (0.48%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pneumonia                                       |                  |                  |  |
| subjects affected / exposed                     | 13 / 208 (6.25%) | 10 / 209 (4.78%) |  |
| occurrences causally related to treatment / all | 3 / 13           | 2 / 11           |  |
| deaths causally related to treatment / all      | 1 / 2            | 0 / 2            |  |
| Postoperative wound infection                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 208 (0.48%)  | 0 / 209 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sepsis                                          |                  |                  |  |
| subjects affected / exposed                     | 2 / 208 (0.96%)  | 0 / 209 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Septic shock                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 208 (0.48%)  | 0 / 209 (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 / 208 (0.00%)  | 1 / 209 (0.48%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urinary tract infection                         |                  |                  |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 208 (0.00%) | 2 / 209 (0.96%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Anal abscess                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 208 (0.48%) | 0 / 209 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Muscle abscess                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 208 (0.00%) | 1 / 209 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abscess neck                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 208 (0.48%) | 0 / 209 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal infection                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 208 (0.00%) | 1 / 209 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intervertebral discitis                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 208 (0.00%) | 1 / 209 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia bacterial                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 208 (0.48%) | 1 / 209 (0.48%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung infection                                  |                 |                 |  |
| subjects affected / exposed                     | 5 / 208 (2.40%) | 1 / 209 (0.48%) |  |
| occurrences causally related to treatment / all | 5 / 5           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal cord abscess                             |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 208 (0.48%) | 0 / 209 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| Infectious pleural effusion                     |                 |                 |  |
| subjects affected / exposed                     | 2 / 208 (0.96%) | 0 / 209 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Cachexia                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 208 (0.48%) | 1 / 209 (0.48%) |  |
| 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 / 208 (0.48%) | 2 / 209 (0.96%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypercalcaemia                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 208 (0.48%) | 4 / 209 (1.91%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 6           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Hypoglycaemia                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 208 (0.00%) | 2 / 209 (0.96%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyponatraemia                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 208 (0.48%) | 1 / 209 (0.48%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Decreased appetite                              |                 |                 |  |
| subjects affected / exposed                     | 6 / 208 (2.88%) | 4 / 209 (1.91%) |  |
| occurrences causally related to treatment / all | 7 / 7           | 3 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Type 1 diabetes mellitus                        |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 208 (0.00%) | 1 / 209 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 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>                     | Active Comparator Arm<br>Docetaxel/Paclitaxel | Nivolumab Arm      |  |
|-------------------------------------------------------|-----------------------------------------------|--------------------|--|
| Total subjects affected by non-serious adverse events |                                               |                    |  |
| subjects affected / exposed                           | 203 / 208 (97.60%)                            | 165 / 209 (78.95%) |  |
| Investigations                                        |                                               |                    |  |
| Weight decreased                                      |                                               |                    |  |
| subjects affected / exposed                           | 11 / 208 (5.29%)                              | 11 / 209 (5.26%)   |  |
| occurrences (all)                                     | 11                                            | 11                 |  |
| Neutrophil count decreased                            |                                               |                    |  |
| subjects affected / exposed                           | 76 / 208 (36.54%)                             | 4 / 209 (1.91%)    |  |
| occurrences (all)                                     | 185                                           | 12                 |  |
| Lymphocyte count decreased                            |                                               |                    |  |
| subjects affected / exposed                           | 21 / 208 (10.10%)                             | 5 / 209 (2.39%)    |  |
| occurrences (all)                                     | 39                                            | 19                 |  |
| Aspartate aminotransferase increased                  |                                               |                    |  |
| subjects affected / exposed                           | 7 / 208 (3.37%)                               | 14 / 209 (6.70%)   |  |
| occurrences (all)                                     | 8                                             | 14                 |  |
| Alanine aminotransferase increased                    |                                               |                    |  |
| subjects affected / exposed                           | 7 / 208 (3.37%)                               | 11 / 209 (5.26%)   |  |
| occurrences (all)                                     | 9                                             | 11                 |  |
| White blood cell count decreased                      |                                               |                    |  |
| subjects affected / exposed                           | 72 / 208 (34.62%)                             | 2 / 209 (0.96%)    |  |
| occurrences (all)                                     | 173                                           | 2                  |  |
| Nervous system disorders                              |                                               |                    |  |
| Neuropathy peripheral                                 |                                               |                    |  |
| subjects affected / exposed                           | 23 / 208 (11.06%)                             | 0 / 209 (0.00%)    |  |
| occurrences (all)                                     | 23                                            | 0                  |  |
| Dysgeusia                                             |                                               |                    |  |

|                                                                                   |                         |                         |  |
|-----------------------------------------------------------------------------------|-------------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                  | 14 / 208 (6.73%)<br>14  | 5 / 209 (2.39%)<br>5    |  |
| Peripheral sensory neuropathy<br>subjects affected / exposed<br>occurrences (all) | 48 / 208 (23.08%)<br>50 | 1 / 209 (0.48%)<br>1    |  |
| Blood and lymphatic system disorders                                              |                         |                         |  |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)                       | 61 / 208 (29.33%)<br>76 | 25 / 209 (11.96%)<br>28 |  |
| Leukopenia<br>subjects affected / exposed<br>occurrences (all)                    | 18 / 208 (8.65%)<br>61  | 0 / 209 (0.00%)<br>0    |  |
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)                   | 40 / 208 (19.23%)<br>94 | 1 / 209 (0.48%)<br>1    |  |
| General disorders and administration<br>site conditions                           |                         |                         |  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)                       | 39 / 208 (18.75%)<br>51 | 29 / 209 (13.88%)<br>40 |  |
| Malaise<br>subjects affected / exposed<br>occurrences (all)                       | 50 / 208 (24.04%)<br>72 | 13 / 209 (6.22%)<br>16  |  |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)                       | 52 / 208 (25.00%)<br>54 | 20 / 209 (9.57%)<br>21  |  |
| Chest pain<br>subjects affected / exposed<br>occurrences (all)                    | 4 / 208 (1.92%)<br>5    | 13 / 209 (6.22%)<br>15  |  |
| Gastrointestinal disorders                                                        |                         |                         |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                      | 17 / 208 (8.17%)<br>17  | 14 / 209 (6.70%)<br>15  |  |
| Stomatitis<br>subjects affected / exposed<br>occurrences (all)                    | 26 / 208 (12.50%)<br>28 | 7 / 209 (3.35%)<br>7    |  |
| Abdominal pain                                                                    |                         |                         |  |

|                                                 |                    |                   |  |
|-------------------------------------------------|--------------------|-------------------|--|
| subjects affected / exposed                     | 8 / 208 (3.85%)    | 13 / 209 (6.22%)  |  |
| occurrences (all)                               | 9                  | 15                |  |
| Constipation                                    |                    |                   |  |
| subjects affected / exposed                     | 40 / 208 (19.23%)  | 36 / 209 (17.22%) |  |
| occurrences (all)                               | 42                 | 36                |  |
| Diarrhoea                                       |                    |                   |  |
| subjects affected / exposed                     | 34 / 208 (16.35%)  | 39 / 209 (18.66%) |  |
| occurrences (all)                               | 36                 | 42                |  |
| Dysphagia                                       |                    |                   |  |
| subjects affected / exposed                     | 3 / 208 (1.44%)    | 13 / 209 (6.22%)  |  |
| occurrences (all)                               | 3                  | 13                |  |
| Nausea                                          |                    |                   |  |
| subjects affected / exposed                     | 40 / 208 (19.23%)  | 23 / 209 (11.00%) |  |
| occurrences (all)                               | 41                 | 26                |  |
| Respiratory, thoracic and mediastinal disorders |                    |                   |  |
| Dyspnoea                                        |                    |                   |  |
| subjects affected / exposed                     | 8 / 208 (3.85%)    | 13 / 209 (6.22%)  |  |
| occurrences (all)                               | 12                 | 13                |  |
| Cough                                           |                    |                   |  |
| subjects affected / exposed                     | 25 / 208 (12.02%)  | 33 / 209 (15.79%) |  |
| occurrences (all)                               | 27                 | 35                |  |
| Skin and subcutaneous tissue disorders          |                    |                   |  |
| Dry skin                                        |                    |                   |  |
| subjects affected / exposed                     | 7 / 208 (3.37%)    | 12 / 209 (5.74%)  |  |
| occurrences (all)                               | 8                  | 12                |  |
| Pruritus                                        |                    |                   |  |
| subjects affected / exposed                     | 15 / 208 (7.21%)   | 26 / 209 (12.44%) |  |
| occurrences (all)                               | 18                 | 29                |  |
| Alopecia                                        |                    |                   |  |
| subjects affected / exposed                     | 100 / 208 (48.08%) | 3 / 209 (1.44%)   |  |
| occurrences (all)                               | 100                | 3                 |  |
| Rash                                            |                    |                   |  |
| subjects affected / exposed                     | 40 / 208 (19.23%)  | 26 / 209 (12.44%) |  |
| occurrences (all)                               | 43                 | 28                |  |
| Psychiatric disorders                           |                    |                   |  |

|                                                                                                                                                                                                 |                                                        |                                                      |  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|------------------------------------------------------|--|
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                    | 13 / 208 (6.25%)<br>14                                 | 12 / 209 (5.74%)<br>12                               |  |
| Endocrine disorders<br>Hypothyroidism<br>subjects affected / exposed<br>occurrences (all)                                                                                                       | 3 / 208 (1.44%)<br>3                                   | 21 / 209 (10.05%)<br>21                              |  |
| Musculoskeletal and connective tissue disorders<br>Myalgia<br>subjects affected / exposed<br>occurrences (all)<br><br>Arthralgia<br>subjects affected / exposed<br>occurrences (all)            | 22 / 208 (10.58%)<br>23<br><br>25 / 208 (12.02%)<br>29 | 6 / 209 (2.87%)<br>6<br><br>10 / 209 (4.78%)<br>12   |  |
| Infections and infestations<br>Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all) | 13 / 208 (6.25%)<br>17<br><br>10 / 208 (4.81%)<br>15   | 15 / 209 (7.18%)<br>34<br><br>13 / 209 (6.22%)<br>18 |  |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all)                                                                                    | 68 / 208 (32.69%)<br>79                                | 40 / 209 (19.14%)<br>42                              |  |

**More information**

**Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? Yes

| Date        | Amendment                                                                                                                                                                                   |
|-------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 24 May 2019 | To include the timing of informed consent from subjects to enter the CA209-473 Extension phase and to set wash-out period before the first CA209-473 dose in the CA209-473 Extension phase. |

Notes:

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**Interruptions (globally)**

Were there any global interruptions to the trial? No

**Limitations and caveats**

None reported