



Clinical trial results:

A Phase III Open-Label, Multicenter Trial of Avelumab (MSB0010718C) Versus Docetaxel in Subjects With Non-Small Cell Lung Cancer That Has Progressed After a Platinum-Containing Doublet

Summary

| | |
|--------------------------|---|
| EudraCT number | 2014-005060-15 |
| Trial protocol | SK DE GB BE HU DK AT ES NL FR CZ PL HR LV |
| Global end of trial date | 03 December 2019 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 05 August 2020 |
| First version publication date | 05 August 2020 |

Trial information

Trial identification

| | |
|-----------------------|---------------|
| Sponsor protocol code | EMR100070-004 |
|-----------------------|---------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02395172 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Merck KGaA, Darmstadt, Germany |
| Sponsor organisation address | Frankfurter Strasse 250, Darmstadt, Germany, 64293 |
| Public contact | Communication Center, Merck KGaA, Darmstadt, Germany, +49 6151725200, service@merckgroup.com |
| Scientific contact | Communication Center, Merck KGaA, Darmstadt, Germany, +49 6151725200, service@merckgroup.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 | 03 December 2019 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|------------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 03 December 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this study was to demonstrate superiority with regards to overall survival of Avelumab versus Docetaxel in subjects with programmed death ligand 1 (PD-L1) positive, non-small cell lung cancer (NSCLC) after failure of a platinum-based doublet.

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 24 March 2015 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 5 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Argentina: 23 |
| Country: Number of subjects enrolled | Australia: 5 |
| Country: Number of subjects enrolled | Belgium: 26 |
| Country: Number of subjects enrolled | Brazil: 26 |
| Country: Number of subjects enrolled | Bulgaria: 18 |
| Country: Number of subjects enrolled | Chile: 22 |
| Country: Number of subjects enrolled | Colombia: 6 |
| Country: Number of subjects enrolled | Croatia: 7 |
| Country: Number of subjects enrolled | Czech Republic: 8 |
| Country: Number of subjects enrolled | Denmark: 9 |
| Country: Number of subjects enrolled | Estonia: 1 |
| Country: Number of subjects enrolled | France: 38 |
| Country: Number of subjects enrolled | Hungary: 16 |
| Country: Number of subjects enrolled | Israel: 1 |
| Country: Number of subjects enrolled | Italy: 57 |
| Country: Number of subjects enrolled | Japan: 101 |
| Country: Number of subjects enrolled | Latvia: 1 |

| | |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Mexico: 10 |
| Country: Number of subjects enrolled | Peru: 13 |
| Country: Number of subjects enrolled | Poland: 67 |
| Country: Number of subjects enrolled | Korea, Republic of: 100 |
| Country: Number of subjects enrolled | Romania: 20 |
| Country: Number of subjects enrolled | Russian Federation: 16 |
| Country: Number of subjects enrolled | South Africa: 3 |
| Country: Number of subjects enrolled | Spain: 36 |
| Country: Number of subjects enrolled | Switzerland: 1 |
| Country: Number of subjects enrolled | Taiwan: 12 |
| Country: Number of subjects enrolled | Turkey: 100 |
| Country: Number of subjects enrolled | United Kingdom: 31 |
| Country: Number of subjects enrolled | United States: 18 |
| Worldwide total number of subjects | 792 |
| EEA total number of subjects | 335 |

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) | 426 |
| From 65 to 84 years | 361 |
| 85 years and over | 5 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

First subject signed informed consent: 24 Mar 2015, Clinical data cut-off: 04 March 2019.

Period 1

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

Arms

| | |
|------------------------------|----------|
| Are arms mutually exclusive? | Yes |
| Arm title | Avelumab |

Arm description:

Subjects received 10 milligram per kilogram (mg/kg) of avelumab as a 1-hour intravenous infusion once every 2 weeks until confirmed disease progression, significant clinical deterioration, unacceptable toxicity, or any criterion for withdrawal from the study or Investigational Medicinal Product (IMP) as defined in the study protocol was fulfilled.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Avelumab |
| Investigational medicinal product code | MSB0010718C |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for solution for infusion |
| Routes of administration | Intravenous bolus use |

Dosage and administration details:

Subjects received intravenous infusion of avelumab at a dose of 10 mg/kg over the duration of 1 hour once every 2 weeks until confirmed disease progression.

| | |
|------------------|-----------|
| Arm title | Docetaxel |
|------------------|-----------|

Arm description:

Subjects received 75 mg per square meter (m^2) (per label) of docetaxel by intravenous infusion once every 3 weeks until confirmed disease progression, significant clinical deterioration, unacceptable toxicity, or any criterion for withdrawal from the study or Investigational Medicinal Product (IMP) as defined in the study protocol was fulfilled.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Docetaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for solution for infusion |
| Routes of administration | Intravenous bolus use |

Dosage and administration details:

Subjects received 75 mg per square meter (m^2) (per label) of docetaxel by intravenous infusion once every 3 weeks until confirmed disease progression.

| Number of subjects in period 1 | Avelumab | Docetaxel |
|---------------------------------------|----------|-----------|
| Started | 396 | 396 |
| Treated | 393 | 365 |
| Completed | 393 | 365 |
| Not completed | 3 | 31 |
| Subjects randomized but not treated | 3 | 31 |

Baseline characteristics

Reporting groups

| | |
|--|-----------|
| Reporting group title | Avelumab |
| Reporting group description: | |
| Subjects received 10 milligram per kilogram (mg/kg) of avelumab as a 1-hour intravenous infusion once every 2 weeks until confirmed disease progression, significant clinical deterioration, unacceptable toxicity, or any criterion for withdrawal from the study or Investigational Medicinal Product (IMP) as defined in the study protocol was fulfilled. | |
| Reporting group title | Docetaxel |
| Reporting group description: | |
| Subjects received 75 mg per square meter (m ²) (per label) of docetaxel by intravenous infusion once every 3 weeks until confirmed disease progression, significant clinical deterioration, unacceptable toxicity, or any criterion for withdrawal from the study or Investigational Medicinal Product (IMP) as defined in the study protocol was fulfilled. | |

| Reporting group values | Avelumab | Docetaxel | Total |
|---|----------|-----------|-------|
| Number of subjects | 396 | 396 | 792 |
| Age categorical Units: Subjects | | | |
| Age Continuous Units: years | | | |
| arithmetic mean | 62.8 | 62.5 | |
| standard deviation | ± 9.99 | ± 9.65 | - |
| Sex: Female, Male Units: Subjects | | | |
| Female | 127 | 123 | 250 |
| Male | 269 | 273 | 542 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 1 | 1 |
| Asian | 102 | 114 | 216 |
| Native Hawaiian or Other Pacific Islander | 1 | 0 | 1 |
| Black or African American | 5 | 1 | 6 |
| White | 273 | 262 | 535 |
| Not collected at the site | 14 | 14 | 28 |
| Other | 1 | 4 | 5 |
| Ethnicity (NIH/OMB) Units: Subjects | | | |
| Hispanic or Latino | 59 | 42 | 101 |
| Not Hispanic or Latino | 297 | 307 | 604 |
| Unknown or Not Reported | 40 | 47 | 87 |

End points

End points reporting groups

| | |
|--|-----------|
| Reporting group title | Avelumab |
| Reporting group description: Subjects received 10 milligram per kilogram (mg/kg) of avelumab as a 1-hour intravenous infusion once every 2 weeks until confirmed disease progression, significant clinical deterioration, unacceptable toxicity, or any criterion for withdrawal from the study or Investigational Medicinal Product (IMP) as defined in the study protocol was fulfilled. | |
| Reporting group title | Docetaxel |
| Reporting group description: Subjects received 75 mg per square meter (m ²) (per label) of docetaxel by intravenous infusion once every 3 weeks until confirmed disease progression, significant clinical deterioration, unacceptable toxicity, or any criterion for withdrawal from the study or Investigational Medicinal Product (IMP) as defined in the study protocol was fulfilled. | |

Primary: Overall Survival (OS) Time in Programmed Death Ligand 1 (PD-L1) + Full Analysis Set Population (FAS)

| | |
|--|--|
| End point title | Overall Survival (OS) Time in Programmed Death Ligand 1 (PD-L1) + Full Analysis Set Population (FAS) |
| End point description: The OS time was defined as the time from randomization to the date of death. The subjects who were still alive at the time of data analysis or who were lost to follow-up OS time was censored at the last recorded date that the subjects was known to be alive before the data cutoff date. OS was measured using Kaplan-Meier (KM) estimates. PD-L1+ FAS included all PD-L1+ tumor subjects who were randomly assigned to trial treatment. The PD-L1+ subjects were with greater than or equal to (\geq) 1 percentage (%) of tumor cells with $\geq 1+$ positive membrane staining intensity for PD-L1 protein. | |
| End point type | Primary |
| End point timeframe: Time from date of randomization up to 1420 days | |

| End point values | Avelumab | Docetaxel | | |
|----------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 264 | 265 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 11.4 (9.4 to 13.8) | 10.6 (8.5 to 12.9) | | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Statistical Analysis: OS in PD-L1 + FAS |
| Comparison groups | Avelumab v Docetaxel |

| | |
|---|-------------------|
| Number of subjects included in analysis | 529 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0721 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.87 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.71 |
| upper limit | 1.05 |

Secondary: Overall Survival (OS) Time in Full Analysis Set Population

| | |
|--|--|
| End point title | Overall Survival (OS) Time in Full Analysis Set Population |
| End point description: | |
| The OS time was defined as the time from randomization to the date of death. The subjects who were still alive at the time of data analysis or who were lost to follow-up OS time was censored at the last recorded date that the subjects was known to be alive before the data cutoff date. OS was measured using Kaplan-Meier (KM) estimates. Full analysis set (FAS) included all subjects who were randomized to study. | |
| End point type | Secondary |
| End point timeframe: | |
| Time from date of randomization up to 1420 days | |

| End point values | Avelumab | Docetaxel | | |
|----------------------------------|--------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 396 | 396 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 10.6 (9.2 to 12.3) | 9.9 (8.1 to 11.9) | | |

Statistical analyses

| | |
|---|---------------------------------|
| Statistical analysis title | Statistical Analysis: OS in FAS |
| Comparison groups | Avelumab v Docetaxel |
| Number of subjects included in analysis | 792 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.9 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.77 |
| upper limit | 1.05 |

Secondary: Progression-Free Survival (PFS) Time in PD-L1+ Full Analysis Set Population

| | |
|-----------------|---|
| End point title | Progression-Free Survival (PFS) Time in PD-L1+ Full Analysis Set Population |
|-----------------|---|

End point description:

PFS was defined as the time from date of randomization until date of the first documentation of progressive disease (PD) or death due to any cause in the absence of documented PD, whichever occurs first. PFS was assessed as per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) as adjudicated by independent endpoint review committee (IERC). PD was defined as at least a 20 percent (%) increase in the sum of longest diameter (SLD), taking as reference the smallest SLD recorded from baseline or the appearance of 1 or more new lesions and unequivocal progression of non-target lesions. PFS was measured using Kaplan-Meier (KM) estimates. PD-L1+ FAS included all PD-L1+ tumor subjects who were randomly assigned to trial treatment. PD-L1+ FAS included all PD-L1+ tumor subjects who were randomly assigned to trial treatment. The PD-L1+ subjects were with ≥ 1 percentage of tumor cells with $\geq 1+$ positive membrane staining intensity for PD-L1 protein.

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

End point timeframe:

Time from date of randomization up to 907 days

| End point values | Avelumab | Docetaxel | | |
|----------------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 264 | 265 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 3.4 (2.7 to 4.9) | 4.1 (3.0 to 5.3) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical Analysis: PFS in PD-L1 + FAS |
| Comparison groups | Avelumab v Docetaxel |
| Number of subjects included in analysis | 529 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8 |
| upper limit | 1.27 |

Secondary: Progression-Free Survival (PFS) Time in Full Analysis Set Population

| | |
|-----------------|--|
| End point title | Progression-Free Survival (PFS) Time in Full Analysis Set Population |
|-----------------|--|

End point description:

PFS was defined as the time from date of randomization until date of the first documentation of progressive disease (PD) or death due to any cause in the absence of documented PD, whichever occurs first. PFS was assessed as per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) as adjudicated by independent endpoint review committee (IERC). PD was defined as at least a 20 percent (%) increase in the sum of longest diameter (SLD), taking as reference the smallest SLD recorded from baseline or the appearance of 1 or more new lesions and unequivocal progression of non-target lesions. PFS was measured using Kaplan-Meier (KM) estimates. Full analysis set (FAS) included all subjects who were randomized to study.

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

End point timeframe:

Time from date of randomization up to 907 days

| End point values | Avelumab | Docetaxel | | |
|----------------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 396 | 396 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 2.8 (2.7 to 3.5) | 4.2 (3.3 to 5.2) | | |

Statistical analyses

| | |
|---|------------------------------------|
| Statistical analysis title | Statistical Analysis of PFS in FAS |
| Comparison groups | Avelumab v Docetaxel |
| Number of subjects included in analysis | 792 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.17 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.98 |
| upper limit | 1.41 |

Secondary: Number of Subjects with Confirmed Best Overall Response (BOR) as Assessed by an Independent Endpoint Review Committee (IERC) in Full Analysis Set Population

| | |
|-----------------|--|
| End point title | Number of Subjects with Confirmed Best Overall Response (BOR) as Assessed by an Independent Endpoint Review Committee (IERC) in Full Analysis Set Population |
|-----------------|--|

End point description:

Confirmed BOR: best response of any of the complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) recorded from the date of randomization until disease progression or recurrence (taking the smallest measurement recorded since the start of treatment as reference). CR: Disappearance of all evidence of target & non-target lesions. PR: At least 30% reduction from baseline in the sum of the longest diameter (SLD) of all lesions. SD: Neither sufficient increase to qualify for PD nor sufficient shrinkage to qualify for PR. PD: a 20% increase in the SLD, taking as reference the smallest SLD recorded from baseline or the appearance of 1 or more new lesions & unequivocal progression of non-target lesions. Number of subjects with best overall response in each category (CR, PR, SD, PD) was reported. FAS was used.

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

End point timeframe:

Time from date of randomization up to 907 days

| End point values | Avelumab | Docetaxel | | |
|--|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 396 | 396 | | |
| Units: subjects | | | | |
| Complete Response | 5 | 2 | | |
| Partial Response | 54 | 42 | | |
| Stable Disease | 129 | 158 | | |
| Non-complete Response/ Non-progressive Disease | 5 | 13 | | |
| Progressive Disease | 150 | 82 | | |
| Not Evaluable | 53 | 99 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Confirmed Best Overall Response (BOR) as Assessed by Independent Endpoint Review Committee (IERC) in PD-L1+ Full Analysis Set Population

| | |
|-----------------|--|
| End point title | Number of Subjects with Confirmed Best Overall Response (BOR) as Assessed by Independent Endpoint Review Committee (IERC) in PD-L1+ Full Analysis Set Population |
|-----------------|--|

End point description:

Confirmed BOR: best response of any of the complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) recorded from the date of randomization until disease progression or recurrence (taking the smallest measurement recorded since the start of treatment as reference). CR: Disappearance of all evidence of target & non-target lesions. PR: At least 30% reduction from baseline in the sum of the longest diameter (SLD) of all lesions. SD: Neither sufficient increase to qualify for PD nor sufficient shrinkage to qualify for PR. PD: a 20% increase in the SLD, taking as reference the smallest SLD recorded from baseline or the appearance of 1 or more new lesions & unequivocal progression of non-target lesions. Number of subjects with best overall response in each category (CR, PR, SD, PD) was reported. PD-L1+FAS was used.

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

End point timeframe:

Time from date of randomization up to 907 days

| End point values | Avelumab | Docetaxel | | |
|--|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 264 | 265 | | |
| Units: subjects | | | | |
| Complete Response | 4 | 1 | | |
| Partial Response | 46 | 30 | | |
| Stable Disease | 86 | 104 | | |
| Non-complete Response/ Non-progressive Disease | 4 | 12 | | |
| Progressive Disease | 93 | 57 | | |
| Not Evaluable | 31 | 61 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Objective Response as Assessed by Independent Endpoint Review Committee (IERC) in Full Analysis Set Population

| | |
|-----------------|--|
| End point title | Percentage of Subjects with Objective Response as Assessed by Independent Endpoint Review Committee (IERC) in Full Analysis Set Population |
|-----------------|--|

End point description:

Percentage of subjects with objective response (CR plus PR) according to RECIST Version 1.1 was reported. CR: Disappearance of all evidence of target and non-target lesions. PR: At least 30% reduction from baseline in the sum of the longest diameter (SLD) of all lesions. Full analysis set (FAS) included all subjects who were randomized to study.

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

End point timeframe:

Time from date of randomization up to 907 days

| End point values | Avelumab | Docetaxel | | |
|----------------------------------|---------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 396 | 396 | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 14.9 (11.5 to 18.8) | 11.1 (8.2 to 14.6) | | |

Statistical analyses

| | |
|-----------------------------------|---------------------------|
| Statistical analysis title | Objective Response in FAS |
| Comparison groups | Avelumab v Docetaxel |

| | |
|---|-----------------|
| Number of subjects included in analysis | 792 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.92 |
| upper limit | 2.13 |

Secondary: Percentage of Subjects with Objective Response as Assessed by Independent Endpoint Review Committee (IERC) in PD-L1+ Full Analysis Set Population

| | |
|-----------------|---|
| End point title | Percentage of Subjects with Objective Response as Assessed by Independent Endpoint Review Committee (IERC) in PD-L1+ Full Analysis Set Population |
|-----------------|---|

End point description:

Percentage of subjects with objective response (CR plus PR) according to RECIST Version 1.1 was reported. CR: Disappearance of all evidence of target and non-target lesions. PR: At least 30% reduction from baseline in the sum of the longest diameter (SLD) of all lesions. PD-L1+ FAS included all PD-L1+ tumor subjects who were randomly assigned to trial treatment. The PD-L1+ subjects were with ≥ 1 percentage of tumor cells with $\geq 1+$ positive membrane staining intensity for PD-L1 protein.

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

End point timeframe:

Time from date of randomization up to 907 days

| End point values | Avelumab | Docetaxel | | |
|----------------------------------|---------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 264 | 265 | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 18.9 (14.4 to 24.2) | 11.7 (8.1 to 16.2) | | |

Statistical analyses

| | |
|---|-----------------------------------|
| Statistical analysis title | Objective Response in PD-L1 + FAS |
| Comparison groups | Avelumab v Docetaxel |
| Number of subjects included in analysis | 529 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.76 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.08 |
| upper limit | 2.86 |

Secondary: Change From Baseline in European Quality of Life 5-dimensions (EQ-5D-5L) Health Outcome Questionnaire Through Composite Index Score at End of Treatment (EOT)

| | |
|-----------------|---|
| End point title | Change From Baseline in European Quality of Life 5-dimensions (EQ-5D-5L) Health Outcome Questionnaire Through Composite Index Score at End of Treatment (EOT) |
|-----------------|---|

End point description:

The EQ-5D-5L health outcome questionnaire was a measure of health status that provides a simple descriptive profile and a single index value. The EQ-5D-5L defined health in terms of mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The 5 items were combined to generate health profiles. These profiles were converted to a continuous single index score. The lowest possible score was -0.59 (unable to walk, unable to self-care, unable to do usual activities, extreme pain or discomfort, extreme anxiety or depression) and the highest score was 1.00 (no problems in all 5 dimensions). Health-related quality of life (HRQoL) analysis set was a subset of the FAS and includes all FAS subjects who had 1 baseline HRQoL assessment and at least 1 post-baseline HRQoL questionnaire completed. Here, "number of subjects analyzed" signified the subjects analyzed in this endpoint.

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

End point timeframe:

Baseline, End of treatment visit (up to Week 124)

| End point values | Avelumab | Docetaxel | | |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 172 | 196 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | -0.1245 (± 0.28021) | -0.0988 (± 0.26615) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Quality of Life 5-dimensions (EQ-5D-5L) Health Outcome Questionnaire Through Visual Analogue Scale (VAS) at End of Treatment (EOT)

| | |
|-----------------|---|
| End point title | Change From Baseline in European Quality of Life 5-dimensions (EQ-5D-5L) Health Outcome Questionnaire Through Visual Analogue Scale (VAS) at End of Treatment (EOT) |
|-----------------|---|

End point description:

EQ-5D-5L was comprised of the following 5 participant-reported dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension had 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The responses were used to derive overall score using a visual analog scale (VAS) that ranged from 0 to 100 millimeter (mm), where 0 (worst health you can imagine) and 100 (best health you can imagine). Health-related quality of life

(HRQoL) analysis set was a subset of the FAS and includes all FAS subjects who had 1 baseline HRQoL assessment and at least 1 post-baseline HRQoL questionnaire completed. Here, "Number of subjects analyzed" signified the subjects analyzed in this endpoint.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, End of treatment visit (up to Week 124) | |

| End point values | Avelumab | Docetaxel | | |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 171 | 196 | | |
| Units: millimeter | | | | |
| arithmetic mean (standard deviation) | -8.1 (\pm 22.06) | -7.0 (\pm 21.12) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organization for the Research and Treatment of Cancer Quality of Life (EORTC QLQ-C30) Global Health Status at End of Treatment (EOT)

| | |
|-----------------|---|
| End point title | Change From Baseline in European Organization for the Research and Treatment of Cancer Quality of Life (EORTC QLQ-C30) Global Health Status at End of Treatment (EOT) |
|-----------------|---|

End point description:

EORTC QLQ-C30 was a 30-question tool used to assess the overall quality of life (QoL) in cancer subjects. It consisted of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, role, cognitive, emotional, social), and 9 symptom scales/items (Fatigue, nausea and vomiting, pain, dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, financial impact). The EORTC QLQ-C30 GHS/QoL score ranged from 0 to 100, where 0 (very poor physical condition and QoL) and 100 (excellent overall physical condition and QoL). Health-related quality of life (HRQoL) analysis set was a subset of the FAS and includes all FAS subjects who had 1 baseline HRQoL assessment and at least 1 post-baseline HRQoL questionnaire completed. Here, "Number of subjects analyzed" signified the subjects analyzed in this endpoint.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, End of treatment visit (up to Week 124) | |

| End point values | Avelumab | Docetaxel | | |
|--------------------------------------|-----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 172 | 196 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | -9.79 (\pm 24.506) | -9.44 (\pm 18.933) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13 (EORTC QLQ-LC13) at End of Treatment (EOT)

| | |
|-----------------|--|
| End point title | Change from Baseline in European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13 (EORTC QLQ-LC13) at End of Treatment (EOT) |
|-----------------|--|

End point description:

EORTC QLQ-LC13 consisted of 13 questions relating to disease symptoms specific to lung cancer and treatment side effects typical of treatment with chemotherapy and radiotherapy. The EORTC QLQ-LC13 module generated one multiple-item scale assessing dyspnea, coughing, hemoptysis, sore mouth, dysphagia, neuropathy, alopecia, pain in chest, pain in arms or shoulder and pain in other parts. Score range: 0 (no burden of symptom domain or single symptom item) to 100 (highest burden of symptoms for symptom domains and single items). Health-related quality of life (HRQoL) analysis set was a subset of the FAS and includes all FAS subjects who had 1 baseline HRQoL assessment and at least 1 post-baseline HRQoL questionnaire completed. Here, "n" signified those subjects who were evaluable for the specified category.

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

End point timeframe:

Baseline, End of treatment visit (up to Week 124)

| End point values | Avelumab | Docetaxel | | |
|---|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 348 | 333 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Dyspnea: (n = 172, 197) | 9.95 (± 22.094) | 8.52 (± 21.285) | | |
| Coughing: (n = 172, 197) | -0.58 (± 30.263) | -2.03 (± 32.582) | | |
| Hemoptysis: (n = 172, 197) | 0.19 (± 14.191) | -0.34 (± 16.832) | | |
| Sore Mouth: (n = 172, 197) | 0.78 (± 17.643) | 3.72 (± 24.920) | | |
| Dysphagia: (n = 172, 197) | 5.62 (± 18.401) | 4.23 (± 21.538) | | |
| Peripheral Neuropathy: (n = 172, 197) | 0.19 (± 20.550) | 9.81 (± 30.015) | | |
| Alopecia: (n = 172, 197) | -3.10 (± 20.789) | 30.80 (± 42.582) | | |
| Pain in Chest: (n = 172, 197) | 4.84 (± 28.993) | 0.34 (± 26.935) | | |
| Pain in Arm or Shoulder: (n = 172, 197) | 5.62 (± 28.852) | 0.85 (± 29.439) | | |
| Pain in Other Parts: (n = 171, 197) | 8.77 (± 34.410) | 6.60 (± 30.978) | | |

Statistical analyses

Secondary: Number of Subjects with Treatment Emergent Adverse Events (TEAEs), Treatment Emergent Serious Adverse Events (TESAEs), Drug Related Treatment Emergent Adverse Events and Treatment Emergent Adverse Events Leading to Death

| | |
|-----------------|--|
| End point title | Number of Subjects with Treatment Emergent Adverse Events (TEAEs), Treatment Emergent Serious Adverse Events (TESAEs), Drug Related Treatment Emergent Adverse Events and Treatment Emergent Adverse Events Leading to Death |
|-----------------|--|

End point description:

An Adverse event (AE) was defined as any unfavorable and unintended sign (including clinically significant abnormal laboratory, vital signs and 12-lead Electrocardiogram findings), symptom, or disease temporally associated with the use of study drug or worsening of pre-existing medical condition, whether or not related to study drug. A serious adverse event (SAE) was an AE that resulted in any of the following outcomes: death; life threatening; persistent/significant disability/incapacity; initial or prolonged in subject hospitalization; congenital anomaly/birth defect or was otherwise considered medically important. Treatment-emergent events between first dose of study drug that were absent before treatment or that worsened relative to pre-treatment state up to 30 days after last administration. TEAEs included both Serious TEAEs and non-serious TEAEs. Safety analysis set included all subjects who were administered at least 1 dose of the Investigational Medicinal Product.

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

End point timeframe:

Time from date of randomization up to 1420 days

| End point values | Avelumab | Docetaxel | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 393 | 365 | | |
| Units: subjects | | | | |
| TEAEs | 375 | 346 | | |
| TESAEs | 167 | 145 | | |
| Drug Related TEAEs | 252 | 313 | | |
| TEAEs Leading to Death | 64 | 51 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Treatment Emergent Adverse Events (TEAEs) by Severity

| | |
|-----------------|---|
| End point title | Number of Subjects with Treatment Emergent Adverse Events (TEAEs) by Severity |
|-----------------|---|

End point description:

Treatment Emergent Adverse Events were graded as per National Cancer Institute Common Terminology Criteria for Adverse Experience version 4.03 (NCI-CTCAE v 4.03). Grade 3 refers to severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care and Activity of daily living (ADL), Grade 4 refers to Life-threatening consequences; where urgent intervention indicated, Grade 5 refers to the death related to adverse event. Safety analysis set included all subjects who were administered at least 1 dose of the Investigational Medicinal Product.

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

End point timeframe:

Time from date of randomization up to 1420 days

| End point values | Avelumab | Docetaxel | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 393 | 365 | | |
| Units: subjects | | | | |
| Grade 3 or Higher | 209 | 247 | | |
| Grade 4 or Higher | 87 | 122 | | |
| Grade 5 | 63 | 51 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Eastern Cooperative Oncology Group (ECOG) Performance: Baseline Score vs. Worst Post-baseline Score

| | |
|-----------------|---|
| End point title | Number of Subjects with Eastern Cooperative Oncology Group (ECOG) Performance: Baseline Score vs. Worst Post-baseline Score |
|-----------------|---|

End point description:

ECOG performance status measured to assess subject's performance status on a scale of 0 to 5, where 0 = Fully active, able to carry on all pre-disease activities without restriction; 1 = Restricted in physically strenuous activity, ambulatory and able to carry out light or sedentary work; 2 = Ambulatory and capable of all selfcare but unable to carry out any work activities; 3 = Capable of only limited self-care, confined to bed/chair for more than 50 percent of waking hours; 4 = Completely disabled, cannot carry on any self-care, totally confined to bed/chair; 5 = dead. The subjects with missing worst post baseline score were also reported. ECOG performance status was reported in terms of number of subjects with Baseline value vs. worst post-baseline value (i.e. highest score) combination. Safety analysis set included all subjects who were administered at least 1 dose of the Investigational Medicinal Product.

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

End point timeframe:

Time from date of randomization up to 1420 days

| End point values | Avelumab | Docetaxel | | |
|---|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 393 | 365 | | |
| Units: subjects | | | | |
| Baseline score 0, worst post-baseline score 0 | 52 | 55 | | |
| Baseline score 0, worst post-baseline score 1 | 67 | 41 | | |
| Baseline score 0, worst post-baseline score 2 | 19 | 12 | | |
| Baseline score 0, worst post-baseline score 3 | 5 | 2 | | |

| | | | | |
|---|-----|-----|--|--|
| Baseline score 0, worst post-baseline score 4 | 0 | 1 | | |
| Baseline score 0, worst post-baseline score 5 | 1 | 0 | | |
| Baseline score 0, worst post-baseline Missing | 0 | 6 | | |
| Baseline score 1, worst post-baseline score 0 | 6 | 1 | | |
| Baseline score 1, worst post-baseline score 1 | 157 | 172 | | |
| Baseline score 1, worst post-baseline score 2 | 47 | 41 | | |
| Baseline score 1, worst post-baseline score 3 | 23 | 8 | | |
| Baseline score 1, worst post-baseline score 4 | 3 | 2 | | |
| Baseline score 1, worst post-baseline score 5 | 1 | 1 | | |
| Baseline score 1, worst post-baseline Missing | 12 | 23 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Positive Anti-Drug Antibodies (ADAs) and Neutralizing Antibodies (NABs) for Avelumab

| | |
|-----------------|---|
| End point title | Number of Subjects with Positive Anti-Drug Antibodies (ADAs) and Neutralizing Antibodies (NABs) for Avelumab ^[1] |
|-----------------|---|

End point description:

Serum samples were analyzed by a validated electrochemiluminescence immunoassay to detect the presence of antidrug antibodies (ADA). Samples that screened positive were subsequently tested in a confirmatory assay. Number of subjects with ADA or nAb positive results for Avelumab were reported. Full analysis set (FAS) included all subjects who were randomized to study. Here, "Number of Subjects Analyzed" signified subjects with at least one valid ADA result at any time point.

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

End point timeframe:

Time from date of randomization up to 1420 days

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint was evaluated for Avelumab arm only.

| End point values | Avelumab | | | |
|-----------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 388 | | | |
| Units: subjects | | | | |
| ADAs to Avelumab | 58 | | | |
| NABs to Avelumab | 14 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Time from date of randomization up to 1420 days

Adverse event reporting additional description:

Safety analysis set included all subjects who were administered at least 1 dose of the Investigational Medicinal Product.

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

Dictionary used

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

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

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Docetaxel |
|-----------------------|-----------|

Reporting group description:

Subjects received 75 mg per square meter (m²) (per label) of docetaxel by intravenous infusion once every 3 weeks until confirmed disease progression, significant clinical deterioration, unacceptable toxicity, or any criterion for withdrawal from the study or Investigational Medicinal Product (IMP) as defined in the study protocol was fulfilled.

| | |
|-----------------------|----------|
| Reporting group title | Avelumab |
|-----------------------|----------|

Reporting group description:

Subjects received 10 milligram per kilogram (mg/kg) of avelumab as a 1-hour intravenous infusion once every 2 weeks until confirmed disease progression, significant clinical deterioration, unacceptable toxicity, or any criterion for withdrawal from the study or Investigational Medicinal Product (IMP) as defined in the study protocol was fulfilled.

| Serious adverse events | Docetaxel | Avelumab | |
|---|--------------------|--------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 145 / 365 (39.73%) | 167 / 393 (42.49%) | |
| number of deaths (all causes) | 297 | 316 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Metastases to central nervous system | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 5 / 393 (1.27%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant pleural effusion | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 2 / 393 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to bone | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 365 (0.00%) | 2 / 393 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colorectal cancer | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| 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 | 1 / 365 (0.27%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Metastases to liver | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to meninges | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastatic neoplasm | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Tumour pain | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Superior vena cava syndrome | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 2 / 393 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic aneurysm | | | |

| | | | |
|--|------------------|-------------------|--|
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intermittent claudication | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 393 (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 | 2 / 365 (0.55%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Disease progression | | | |
| subjects affected / exposed | 26 / 365 (7.12%) | 41 / 393 (10.43%) | |
| occurrences causally related to treatment / all | 0 / 26 | 0 / 41 | |
| deaths causally related to treatment / all | 0 / 20 | 0 / 32 | |
| Asthenia | | | |
| subjects affected / exposed | 3 / 365 (0.82%) | 6 / 393 (1.53%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 4 / 365 (1.10%) | 6 / 393 (1.53%) | |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 6 | |
| deaths causally related to treatment / all | 1 / 4 | 0 / 6 | |
| Pain | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 365 (0.27%) | 2 / 393 (0.51%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chills | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fatigue | | | |
| subjects affected / exposed | 3 / 365 (0.82%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malaise | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mucosal inflammation | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 2 / 365 (0.55%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 365 (0.55%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Sudden cardiac death | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 2 / 393 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 7 / 365 (1.92%) | 11 / 393 (2.80%) | |
| occurrences causally related to treatment / all | 2 / 7 | 0 / 11 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 3 | |
| Pleural effusion | | | |
| subjects affected / exposed | 3 / 365 (0.82%) | 10 / 393 (2.54%) | |
| occurrences causally related to treatment / all | 0 / 3 | 2 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 3 / 365 (0.82%) | 6 / 393 (1.53%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 5 / 393 (1.27%) | |
| occurrences causally related to treatment / all | 1 / 1 | 5 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Pulmonary embolism | | | |
| subjects affected / exposed | 3 / 365 (0.82%) | 4 / 393 (1.02%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| Haemoptysis | | | |
| subjects affected / exposed | 4 / 365 (1.10%) | 3 / 393 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 3 / 365 (0.82%) | 3 / 393 (0.76%) | |
| occurrences causally related to treatment / all | 3 / 3 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Respiratory failure | | | |
| subjects affected / exposed | 3 / 365 (0.82%) | 3 / 393 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 3 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 2 | 1 / 2 | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 2 / 365 (0.55%) | 2 / 393 (0.51%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 1 | |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 2 / 393 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Asphyxia | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Atelectasis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hydrothorax | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Oesophagobronchial fistula | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Bronchial obstruction | | | |
| subjects affected / exposed | 2 / 365 (0.55%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysphonia | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia aspiration | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 365 (0.27%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cystic lung cancer | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 2 / 393 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Agitation | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| 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 | 4 / 365 (1.10%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|------------------|--|
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Infusion related reaction | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 10 / 393 (2.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 10 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 2 / 393 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain contusion | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal compression fracture | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 3 / 393 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 3 / 393 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 2 / 393 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Autoimmune myocarditis | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiac failure acute | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Cardiac tamponade | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 365 (0.00%) | 2 / 393 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiomyopathy | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arrhythmia supraventricular | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiovascular insufficiency | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Depressed level of consciousness | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 365 (0.00%) | 2 / 393 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Balance disorder | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hemiparesis | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hemiplegia | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neurotoxicity | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post herpetic neuralgia | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Syncope | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral infarction | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Loss of consciousness | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paraesthesia | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal cord compression | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombotic cerebral infarction | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 3 / 365 (0.82%) | 4 / 393 (1.02%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile bone marrow aplasia | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 393 (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 | 22 / 365 (6.03%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 21 / 22 | 0 / 0 | |
| deaths causally related to treatment / all | 2 / 2 | 0 / 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 3 / 365 (0.82%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 10 / 365 (2.74%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 10 / 10 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 3 / 393 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 3 / 393 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Ascites | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 5 / 365 (1.37%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 5 / 5 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis erosive | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal pain | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Melaena | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subileus | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysphagia | | | |
| subjects affected / exposed | 2 / 365 (0.55%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus paralytic | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal perforation | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 393 (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 / 365 (0.55%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis ulcerative | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholangitis | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| 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 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| 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 | | | |
| Angioedema | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Henoch-Schonlein purpura | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 393 (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 | 2 / 365 (0.55%) | 3 / 393 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal impairment | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Renal failure | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Autoimmune thyroiditis | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| 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 | | | |
| Back pain | | | |
| subjects affected / exposed | 2 / 365 (0.55%) | 2 / 393 (0.51%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoporotic fracture | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|------------------|-----------------|--|
| Bone pain | | | |
| subjects affected / exposed | 2 / 365 (0.55%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pathological fracture | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 393 (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 | | | |
| Pneumonia | | | |
| subjects affected / exposed | 19 / 365 (5.21%) | 9 / 393 (2.29%) | |
| occurrences causally related to treatment / all | 9 / 19 | 0 / 9 | |
| deaths causally related to treatment / all | 3 / 5 | 0 / 3 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 5 / 365 (1.37%) | 4 / 393 (1.02%) | |
| occurrences causally related to treatment / all | 2 / 5 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infection | | | |
| subjects affected / exposed | 2 / 365 (0.55%) | 3 / 393 (0.76%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 2 / 365 (0.55%) | 2 / 393 (0.51%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Encephalitis | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infective exacerbation of chronic obstructive airways disease | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural infection | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pneumonia streptococcal | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Postoperative wound infection | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 4 / 365 (1.10%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic gangrene | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 2 / 365 (0.55%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Klebsiella infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 4 / 365 (1.10%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningitis | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic infection | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 2 / 365 (0.55%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonitis | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumocystis jirovecii pneumonia | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 5 / 365 (1.37%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 2 / 4 | 0 / 0 | |
| Serratia infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Soft tissue infection | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Streptococcal infection | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 393 (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 | 2 / 365 (0.55%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 3 / 393 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 3 / 393 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperkalaemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 365 (0.00%) | 2 / 393 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 393 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 2 / 365 (0.55%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Electrolyte imbalance | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypophagia | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 393 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Docetaxel | Avelumab | |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 307 / 365 (84.11%) | 320 / 393 (81.42%) | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 66 / 365 (18.08%) | 70 / 393 (17.81%) | |
| occurrences (all) | 66 | 70 | |
| Asthenia | | | |
| subjects affected / exposed | 64 / 365 (17.53%) | 55 / 393 (13.99%) | |
| occurrences (all) | 64 | 55 | |
| Pyrexia | | | |
| subjects affected / exposed | 33 / 365 (9.04%) | 50 / 393 (12.72%) | |
| occurrences (all) | 33 | 50 | |
| Chills | | | |
| subjects affected / exposed | 3 / 365 (0.82%) | 29 / 393 (7.38%) | |
| occurrences (all) | 3 | 29 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 37 / 365 (10.14%) | 21 / 393 (5.34%) | |
| occurrences (all) | 37 | 21 | |
| Malaise | | | |
| subjects affected / exposed | 26 / 365 (7.12%) | 9 / 393 (2.29%) | |
| occurrences (all) | 26 | 9 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 22 / 365 (6.03%) | 5 / 393 (1.27%) | |
| occurrences (all) | 22 | 5 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 46 / 365 (12.60%) | 77 / 393 (19.59%) | |
| occurrences (all) | 46 | 77 | |
| Dyspnoea | | | |
| subjects affected / exposed | 54 / 365 (14.79%) | 75 / 393 (19.08%) | |
| occurrences (all) | 54 | 75 | |
| Productive cough | | | |
| subjects affected / exposed | 8 / 365 (2.19%) | 25 / 393 (6.36%) | |
| occurrences (all) | 8 | 25 | |
| Haemoptysis | | | |

| | | | |
|---|--|--|--|
| subjects affected / exposed occurrences (all) | 15 / 365 (4.11%) 15 | 25 / 393 (6.36%) 25 | |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 22 / 365 (6.03%) 22 | 19 / 393 (4.83%) 19 | |
| Investigations Weight decreased subjects affected / exposed occurrences (all) Neutrophil count decreased subjects affected / exposed occurrences (all) White blood cell count decreased subjects affected / exposed occurrences (all) | 30 / 365 (8.22%) 30 34 / 365 (9.32%) 34 21 / 365 (5.75%) 21 | 50 / 393 (12.72%) 50 3 / 393 (0.76%) 3 2 / 393 (0.51%) 2 | |
| Injury, poisoning and procedural complications Infusion related reaction subjects affected / exposed occurrences (all) | 8 / 365 (2.19%) 8 | 56 / 393 (14.25%) 56 | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) Neuropathy peripheral subjects affected / exposed occurrences (all) Peripheral sensory neuropathy subjects affected / exposed occurrences (all) Dysgeusia subjects affected / exposed occurrences (all) | 19 / 365 (5.21%) 19 33 / 365 (9.04%) 33 27 / 365 (7.40%) 27 23 / 365 (6.30%) 23 | 30 / 393 (7.63%) 30 6 / 393 (1.53%) 6 3 / 393 (0.76%) 3 1 / 393 (0.25%) 1 | |
| Blood and lymphatic system disorders Anaemia | | | |

| | | | |
|--|-------------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 81 / 365 (22.19%) 81 | 50 / 393 (12.72%) 50 | |
| Neutropenia subjects affected / exposed occurrences (all) | 48 / 365 (13.15%) 48 | 2 / 393 (0.51%) 2 | |
| Gastrointestinal disorders | | | |
| Nausea subjects affected / exposed occurrences (all) | 57 / 365 (15.62%) 57 | 56 / 393 (14.25%) 56 | |
| Constipation subjects affected / exposed occurrences (all) | 43 / 365 (11.78%) 43 | 45 / 393 (11.45%) 45 | |
| Vomiting subjects affected / exposed occurrences (all) | 28 / 365 (7.67%) 28 | 38 / 393 (9.67%) 38 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 67 / 365 (18.36%) 67 | 44 / 393 (11.20%) 44 | |
| Stomatitis subjects affected / exposed occurrences (all) | 42 / 365 (11.51%) 42 | 9 / 393 (2.29%) 9 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash subjects affected / exposed occurrences (all) | 17 / 365 (4.66%) 17 | 33 / 393 (8.40%) 33 | |
| Pruritus subjects affected / exposed occurrences (all) | 13 / 365 (3.56%) 13 | 26 / 393 (6.62%) 26 | |
| Alopecia subjects affected / exposed occurrences (all) | 97 / 365 (26.58%) 97 | 3 / 393 (0.76%) 3 | |
| Endocrine disorders | | | |
| Hypothyroidism subjects affected / exposed occurrences (all) | 1 / 365 (0.27%) 1 | 24 / 393 (6.11%) 24 | |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|------------------------------------|-------------------|-------------------|--|
| Back pain | | | |
| subjects affected / exposed | 17 / 365 (4.66%) | 47 / 393 (11.96%) | |
| occurrences (all) | 17 | 47 | |
| Arthralgia | | | |
| subjects affected / exposed | 30 / 365 (8.22%) | 27 / 393 (6.87%) | |
| occurrences (all) | 30 | 27 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 15 / 365 (4.11%) | 25 / 393 (6.36%) | |
| occurrences (all) | 15 | 25 | |
| Pain in extremity | | | |
| subjects affected / exposed | 12 / 365 (3.29%) | 23 / 393 (5.85%) | |
| occurrences (all) | 12 | 23 | |
| Myalgia | | | |
| subjects affected / exposed | 43 / 365 (11.78%) | 17 / 393 (4.33%) | |
| occurrences (all) | 43 | 17 | |
| Infections and infestations | | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 12 / 365 (3.29%) | 28 / 393 (7.12%) | |
| occurrences (all) | 12 | 28 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 76 / 365 (20.82%) | 79 / 393 (20.10%) | |
| occurrences (all) | 76 | 79 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 05 May 2015 | - Added language regarding the predicted number of deaths due to NSCLC in the EU in 2014. - Added language to inclusion criterion 13 for subjects being treated with docetaxel to use effective contraception for up to 3 months after docetaxel treatment and to advise male subjects not to father a child during the 3 months after treatment with docetaxel and to seek advice on conservation of sperm prior to treatment. |
| 10 July 2015 | – Excluded further enrollment of NSCLC subjects with EGFR mutations. – Modified language in Exclusion criterion 4 such that prior therapy with cancer vaccine was no longer allowed. – Changed the duration of treatment for subjects with a confirmed CR to a maximum of 24 months. – Modified AE and SAE follow-up language such that subjects with an AE ongoing at the time of the End-of-Treatment visit must be followed up until the Safety follow-up visit and subjects with a SAE ongoing at the Long term follow-up visit must be followed up by the Investigator until stabilization or until outcome was known, unless the subject was documented as "lost to follow-up. – Changed the bilirubin inclusion criterion from 1.0 x ULN to 1.5 x ULN. – Modified hepatitis testing to include type of test. – Modified mandatory chest CT to allow MRI of the chest to account for regions where CT may be prohibited. – Added language stipulating that complete blood count and core chemistry samples must be drawn and results reviewed within 48 hours prior to IMP administration. – Deleted patient-reported outcome / quality-of-life assessments from the Safety Follow-up and Long-term Follow-up visits. – Added language allowing corticosteroid use in subjects randomized to docetaxel. – Added vaccines to the list of prohibited medications. – Added PK sampling at the End-of-Treatment visit and ADA sampling at the Safety Follow-up visit. |
| 15 November 2016 | – Increased the number of subject to be randomized in the study by 100 due to the new (lower) estimation of the proportion of subjects with PD-L1+ tumors and updated the proportion expected to have PD-L1+ tumors from 80% to 70%. – Updated language regarding tumor assessments so that after 1 year (Week 55) from the start of treatment, assessments would be every 12 weeks (rather than every 6 weeks). – Changed Human Antihuman Antibody (HAHA) to ADA throughout the protocol. – Corrected discrepancies in PK sampling between the text and the Schedule of Assessments – Updated contraception language in the Inclusion Criteria to harmonize with the rest of the avelumab program. – Deleted requirement for subjects with repeated Grade 2 IRRs and ADRs to be withdrawn from treatment. – Updated language on timing of when weight should be determined for dose calculation in order to give more flexibility to Investigators – Deleted bisphosphonate and denosumab from list of nonpermissible medications. – Added language to allow subjects with brain metastases to continue treatment if they fulfilled outlined criteria. – Added guidelines for the management of suspected cardiac-related Immune-related adverse event (irAEs). – Changed definition of overdose from $\geq 5\%$ to $\geq 10\%$ of calculated dose. – Deleted blood sample collection for Adrenocorticotrophic hormone (ACTH), Antinuclear antibody (ANA), Antineutrophil cytoplasmic antibody (ANCA) and rheumatoid factor from End of Treatment and Safety Follow-up visits – Deleted the PP analysis set and any associated analyses – Replaced the ITT population with the FAS |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported