# Clinical trial results:
# An Open Label, Randomized Phase 3 Clinical Trial of Nivolumab vs Therapy of Investigator's Choice in Recurrent or Metastatic Platinum-refractory Squamous Cell Carcinoma of the Head and Neck (SCCHN)

## Summary

| | |
|---|---|
| EudraCT number | 2013-003622-86 |
| Trial protocol | IT GB ES DE NL FR |
| Global end of trial date | 10 September 2021 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 22 September 2022 |
| First version publication date | 22 September 2022 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | CA209-141 |

### Additional study identifiers

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

Notes:

### Sponsors

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

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 19 October 2021 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 10 September 2021 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To compare OS of Nivolumab to Investigator’s Choice in subjects who have tumor progression within 6 months of last dose of platinum therapy in the primary, recurrent, or metastatic setting.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 29 May 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Argentina: 4 |
| Country: Number of subjects enrolled | Brazil: 7 |
| Country: Number of subjects enrolled | Canada: 6 |
| Country: Number of subjects enrolled | France: 52 |
| Country: Number of subjects enrolled | Germany: 28 |
| Country: Number of subjects enrolled | Hong Kong: 1 |
| Country: Number of subjects enrolled | Italy: 25 |
| Country: Number of subjects enrolled | Japan: 27 |
| Country: Number of subjects enrolled | Korea, Democratic People's Republic of: 1 |
| Country: Number of subjects enrolled | Netherlands: 7 |
| Country: Number of subjects enrolled | Spain: 18 |
| Country: Number of subjects enrolled | Switzerland: 7 |
| Country: Number of subjects enrolled | Taiwan: 5 |
| Country: Number of subjects enrolled | United Kingdom: 34 |
| Country: Number of subjects enrolled | United States: 139 |
| Worldwide total number of subjects | 361 |
| EEA total number of subjects | 130 |

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) | 248 |
| From 65 to 84 years | 113 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

361 participants randomized and 347 treated

### Period 1

| | |
|---|---|
| Period 1 title | Pre-Treatment |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Nivolumab 3mg/kg |

Arm description:

Nivolumab was provided at a dose of 3 milligrams/kilogram (mg/kg) using an intravenous (IV) solution for Injection every 2 weeks until disease progression.

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

Dosage and administration details:

3mg/kg every 2 weeks

| | |
|---|---|
| **Arm title** | Investigators Choice |

Arm description:

Participants were provided a dose of Cetuximab intravenous (IV) solution for injection at a dose of 400 milligrams per square meter (mg/m^2) for the first dose followed that a doses of 250 mg/m^2 weekly until disease progression OR a Methotrexate intravenous (IV) solution for Injection at a dose of 40 or 60 mg/m^2 weekly until disease progression OR a Docetaxel intravenous (IV) solution for Injection at a dose of 30 or 40 mg/m^2 weekly until disease progression. The decision regarding which treatment the participant received was at the discretion of the investigator and referred to as Investigators Choice

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

Dosage and administration details:

30mg/m^2 weekly

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

Dosage and administration details:

400mg/m^2 once then 250mg/m^2 weekly

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

Dosage and administration details:

40mg/m^2 weekly, may be increased to 60mg/m^2 if tolerated

| **Number of subjects in period 1** | Nivolumab 3mg/kg | Investigators Choice |
|---|---|---|
| Started | 240 | 121 |
| Completed | 236 | 111 |
| Not completed | 4 | 10 |
| Participant withdrew consent | - | 6 |
| Participant no longer meets study criteria | 2 | 2 |
| Disease Progression | 1 | - |
| Participant request to discontinue study treatment | 1 | 2 |

## Period 2

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

## Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Nivolumab 3mg/kg |

Arm description:

Nivolumab was provided at a dose of 3 milligrams/kilogram (mg/kg) using an intravenous (IV) solution for Injection every 2 weeks until disease progression.

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

Dosage and administration details:

3mg/kg every 2 weeks

| | |
|---|---|
| **Arm title** | Investigators Choice |

Arm description:

Participants were provided a dose of Cetuximab intravenous (IV) solution for injection at a dose of 400 milligrams per square meter (mg/m^2) for the first dose followed that a doses of 250 mg/m^2 weekly until disease progression OR a Methotrexate intravenous (IV) solution for Injection at a dose of 40 or 60 mg/m^2 weekly until disease progression OR a Docetaxel intravenous (IV) solution for Injection at a

dose of 30 or 40 mg/m^2 weekly until disease progression. The decision regarding which treatment the participant received was at the discretion of the investigator and referred to as Investigators Choice

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Docetaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details:<br>30mg/m^2 weekly | |
| Investigational medicinal product name | Methotrexate |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details:<br>40mg/m^2 weekly, may be increased to 60mg/m^2 if tolerated | |
| Investigational medicinal product name | Cetuximab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details:<br>400mg/m^2 once then 250mg/m^2 weekly | |

| **Number of subjects in period 2** | Nivolumab 3mg/kg | Investigators Choice |
|---|---|---|
| Started | 236 | 111 |
| Completed | 1 | 0 |
| Not completed | 235 | 111 |
| Participant withdrew consent | 5 | 1 |
| Maximum Clinical Benefit | 1 | 3 |
| Adverse event unrelated to study drug | 19 | 3 |
| Participant no longer meets study criteria | 1 | - |
| Other reasons | 1 | - |
| Poor/Non-compliance | - | 1 |
| Study Drug Toxicity | 14 | 10 |
| Lost to follow-up | 1 | - |
| Disease Progression | 185 | 87 |
| Participant request to discontinue study treatment | 8 | 6 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Nivolumab 3mg/kg |
| Reporting group description: | |
| Nivolumab was provided at a dose of 3 milligrams/kilogram (mg/kg) using an intravenous (IV) solution for Injection every 2 weeks until disease progression. | |
| Reporting group title | Investigators Choice |
| Reporting group description: | |
| Participants were provided a dose of Cetuximab intravenous (IV) solution for injection at a dose of 400 milligrams per square meter (mg/m^2) for the first dose followed that a doses of 250 mg/m^2 weekly until disease progression OR a Methotrexate intravenous (IV) solution for Injection at a dose of 40 or 60 mg/m^2 weekly until disease progression OR a Docetaxel intravenous (IV) solution for Injection at a dose of 30 or 40 mg/m^2 weekly until disease progression. The decision regarding which treatment the participant received was at the discretion of the investigator and referred to as Investigators Choice | |

| Reporting group values | Nivolumab 3mg/kg | Investigators Choice | Total |
|---|---|---|---|
| Number of subjects | 240 | 121 | 361 |
| Age Categorical<br>Units: Participants | | | |
| < 65 years | 172 | 76 | 248 |
| >=65 and <75 years | 56 | 39 | 95 |
| >=75 years | 12 | 6 | 18 |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 59.0 | 59.4 | |
| standard deviation | ± 10.15 | ± 11.00 | - |
| Sex: Female, Male<br>Units: | | | |
| Female | 43 | 18 | 61 |
| Male | 197 | 103 | 300 |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| White | 196 | 104 | 300 |
| Black or African American | 10 | 3 | 13 |
| Asian | 29 | 14 | 43 |
| Other | 5 | 0 | 5 |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| Hispanic/Latino | 9 | 4 | 13 |
| Not Hispanic/Latino | 132 | 60 | 192 |
| Not Reported | 99 | 57 | 156 |

## End points

### End points reporting groups

| Reporting group title | Nivolumab 3mg/kg |
|---|---|

Reporting group description:

Nivolumab was provided at a dose of 3 milligrams/kilogram (mg/kg) using an intravenous (IV) solution for Injection every 2 weeks until disease progression.

| Reporting group title | Investigators Choice |
|---|---|

Reporting group description:

Participants were provided a dose of Cetuximab intravenous (IV) solution for injection at a dose of 400 milligrams per square meter (mg/m^2) for the first dose followed that a doses of 250 mg/m^2 weekly until disease progression OR a Methotrexate intravenous (IV) solution for Injection at a dose of 40 or 60 mg/m^2 weekly until disease progression OR a Docetaxel intravenous (IV) solution for Injection at a dose of 30 or 40 mg/m^2 weekly until disease progression. The decision regarding which treatment the participant received was at the discretion of the investigator and referred to as Investigators Choice

| Reporting group title | Nivolumab 3mg/kg |
|---|---|

Reporting group description:

Nivolumab was provided at a dose of 3 milligrams/kilogram (mg/kg) using an intravenous (IV) solution for Injection every 2 weeks until disease progression.

| Reporting group title | Investigators Choice |
|---|---|

Reporting group description:

Participants were provided a dose of Cetuximab intravenous (IV) solution for injection at a dose of 400 milligrams per square meter (mg/m^2) for the first dose followed that a doses of 250 mg/m^2 weekly until disease progression OR a Methotrexate intravenous (IV) solution for Injection at a dose of 40 or 60 mg/m^2 weekly until disease progression OR a Docetaxel intravenous (IV) solution for Injection at a dose of 30 or 40 mg/m^2 weekly until disease progression. The decision regarding which treatment the participant received was at the discretion of the investigator and referred to as Investigators Choice

### Primary: Overall Survival (OS)

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

End point description:

OS was defined as the time from randomization to the date of death from any cause. Participants were censored at the date they were last known to be alive and at the date of randomization if they were randomized but had no follow-up. Median OS time was calculated using Kaplan-Meier (KM) method.

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

End point timeframe:

From date of randomization to date of death (Up to approximately 18 months)

| End point values | Nivolumab 3mg/kg | Investigators Choice | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 240 | 121 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 7.49 (5.49 to 9.10) | 5.06 (4.04 to 6.05) | | |

## Statistical analyses

| Statistical analysis title | OS HR |
|---|---|

Statistical analysis description:

Stratified Cox proportional hazard model. HR = Nivolumab over investigator's choice therapy (Cetuximab, Methotrexate, or Docetaxel)

| | |
|---|---|
| Comparison groups | Nivolumab 3mg/kg v Investigators Choice |
| Number of subjects included in analysis | 361 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0101 [1] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.53 |
| upper limit | 0.92 |

Notes:

[1] - Log-rank Test stratified by prior treatment with cetuximab (yes, no) as entered into the Interactive Voice Response System (IVRS). For OS the boundary for statistical significance requires the p-value to be less than 0.0227.

## Secondary: Investigator-Assessed Progression-Free Survival (PFS)

| End point title | Investigator-Assessed Progression-Free Survival (PFS) |
|---|---|

End point description:

PFS was defined as the time between the date of randomization and the first date of documented progression, as determined by the investigator (as per Response Evaluation Criteria In Solid Tumors (RECIST1.1)), or death due to any cause, whichever occurs first. Progressive Disease: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. The sum must demonstrate an absolute increase of at least 5mm. Participants who:
- Die without a reported progression were considered to have progressed on the date of their death.
- Did not progress or die were censored on the date of their last evaluable tumor assessment.
- Without any on study tumor assessments and did not die were censored on their date of randomization.
- Received subsequent systemic anti-cancer therapy prior to documented progression were censored at the date of the last tumor assessment prior to the initiation of the new therapy.

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

End point timeframe:

From date of randomization to date of disease progression or death, whichever occurs first (Up to approximately 87 months)

| End point values | Nivolumab 3mg/kg | Investigators Choice | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 240 | 121 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 2.04 (1.91 to 2.14) | 2.33 (1.94 to 3.06) | | |

## Statistical analyses

| Statistical analysis title | PFS HR |
|---|---|
| Comparison groups | Nivolumab 3mg/kg v Investigators Choice |
| Number of subjects included in analysis | 361 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.86 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.68 |
| upper limit | 1.1 |

## Secondary: Investigator-Assessed Objective Response Rate (ORR)

| End point title | Investigator-Assessed Objective Response Rate (ORR) |
|---|---|

End point description:

ORR was defined as the percentage of randomized participants who achieved a best response of complete response (CR) or partial response (PR) using the RECIST1.1 criteria as per investigator assessment. Complete Response (CR): Disappearance of all target lesions. Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions.

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

End point timeframe:

From date of randomization to date of disease progression or study drug is discontinued, whichever occurs first (Up to approximately 87 months)

| End point values | Nivolumab 3mg/kg | Investigators Choice | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 240 | 121 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 13.3 (9.3 to 18.3) | 5.8 (2.4 to 11.6) | | |

### Statistical analyses

| Statistical analysis title | Difference in ORR |
|---|---|
| Comparison groups | Nivolumab 3mg/kg v Investigators Choice |
| Number of subjects included in analysis | 361 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Difference in ORR |
| Point estimate | 7.6 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.5 |
| upper limit | 13.6 |

| **Statistical analysis title** | ORR Odds Ratio |
|---|---|
| Comparison groups | Nivolumab 3mg/kg v Investigators Choice |
| Number of subjects included in analysis | 361 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | CMH Estimate of Common Odds Ratio |
| Point estimate | 2.49 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.07 |
| upper limit | 5.82 |

## Post-hoc: Overall Survival (OS) - Extended Collection

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

End point description:

OS was defined as the time from randomization to the date of death from any cause. Participants were censored at the date they were last known to be alive and at the date of randomization if they were randomized but had no follow-up. Median OS time was calculated using Kaplan-Meier (KM) method. Note: This outcome measure represents an updated version of the primary endpoint to include additional data collection that has occurred after the primary completion date. (Assessments were made until 10-Sep-2021)

| End point type | Post-hoc |
|---|---|

End point timeframe:

From date of randomization to date of death (Up to approximately 87 months)

| **End point values** | Nivolumab 3mg/kg | Investigators Choice | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 240 | 121 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 7.72 (5.68 to 8.74) | 5.06 (4.04 to 6.24) | | |

## Statistical analyses

| **Statistical analysis title** | OS HR |
|---|---|
| Comparison groups | Nivolumab 3mg/kg v Investigators Choice |
| Number of subjects included in analysis | 361 |
| Analysis specification | Post-hoc |
| Analysis type | |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.68 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.54 |
| upper limit | 0.85 |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AEs and SAEs were monitored from first dose to 100 days post last dose (Up to a max of approximately 70 months). Participants were assessed for Deaths (all causes) from their date of first treatment until study completion (up to approximately 87 months)

Adverse event reporting additional description:

Total number of subjects exposed represents all participants that received at least 1 dose of study medication. Of the randomized population that did not receive any study medication, 1 participant randomized in Nivolumab arm died and 9 participants randomized in Investigator's Choice arm died.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 24.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Investigators Choice |

Reporting group description:

Participants were provided a dose of Cetuximab intravenous (IV) solution for injection at a dose of 400 milligrams per square meter (mg/m^2) for the first dose followed that a doses of 250 mg/m^2 weekly until disease progression OR a Methotrexate intravenous (IV) solution for Injection at a dose of 40 or 60 mg/m^2 weekly until disease progression OR a Docetaxel intravenous (IV) solution for Injection at a dose of 30 or 40 mg/m^2 weekly until disease progression. The decision regarding which treatment the participant received was at the discretion of the investigator and referred to as Investigators Choice

| | |
|---|---|
| Reporting group title | Nivolumab 3mg/kg |

Reporting group description:

Nivolumab was provided at a dose of 3 milligrams/kilogram (mg/kg) using an intravenous (IV) solution for Injection every 2 weeks until disease progression.

| **Serious adverse events** | Investigators Choice | Nivolumab 3mg/kg | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 87 / 111 (78.38%) | 165 / 236 (69.92%) | |
| number of deaths (all causes) | 110 | 219 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Acute myeloid leukaemia | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cancer pain | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Head and neck cancer | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| 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 | 55 / 111 (49.55%) | 94 / 236 (39.83%) | |
| occurrences causally related to treatment / all | 0 / 57 | 0 / 96 | |
| deaths causally related to treatment / all | 0 / 55 | 0 / 92 | |
| Malignant pleural effusion | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to central nervous system | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neoplasm malignant | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour haemorrhage | | | |
| subjects affected / exposed | 3 / 111 (2.70%) | 2 / 236 (0.85%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| Tumour pain | | | |
| subjects affected / exposed | 4 / 111 (3.60%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhage | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 2 / 236 (0.85%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hypertensive urgency | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypovolaemic shock | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shock haemorrhagic | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Superior vena cava syndrome | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Venous thrombosis | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 111 (1.80%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Catheter site pain | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chills | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Face oedema | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 3 / 236 (1.27%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Localised oedema | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malaise | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 111 (1.80%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 4 / 111 (3.60%) | 5 / 236 (2.12%) | |
| occurrences causally related to treatment / all | 2 / 6 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ulcer haemorrhage | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Immune system disorders | | | |
| Contrast media allergy | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eosinophilic granulomatosis with polyangiitis | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchopneumopathy | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|---|---|---|
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 2 / 236 (0.85%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Cough | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoptysis | | | |
| subjects affected / exposed | 2 / 111 (1.80%) | 3 / 236 (1.27%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Emphysema | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 111 (1.80%) | 11 / 236 (4.66%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 12 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Laryngeal oedema | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Laryngeal stenosis | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Obstructive airways disorder | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pharyngeal oedema | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 3 / 111 (2.70%) | 2 / 236 (0.85%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 4 / 111 (3.60%) | 10 / 236 (4.24%) | |
| occurrences causally related to treatment / all | 0 / 4 | 1 / 10 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 2 / 236 (0.85%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pneumothorax spontaneous | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory distress | | | |
| subjects affected / exposed | 3 / 111 (2.70%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 5 / 236 (2.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Stridor | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 2 / 236 (0.85%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Agoraphobia | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Delirium | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Confusional state | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Suicide attempt | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Product issues | | | |
| Device leakage | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device occlusion | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical condition abnormal | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver function test abnormal | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver function test increased | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Platelet count decreased | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| 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 | | | |
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infusion related reaction | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 3 / 236 (1.27%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 2 / 236 (0.85%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Procedural haemorrhage | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shunt thrombosis | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tracheostomy malfunction | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular pseudoaneurysm ruptured | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound haemorrhage | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| Tracheo-oesophageal fistula | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial flutter | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Cardiac arrest | | | |
| subjects affected / exposed | 3 / 111 (2.70%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 2 / 236 (0.85%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiovascular disorder | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pericarditis | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cerebral ischaemia | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |
| subjects affected / exposed | 2 / 111 (1.80%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Focal dyscognitive seizures | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Encephalopathy | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydrocephalus | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Neuralgia | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 111 (0.90%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Speech disorder | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Radiculopathy | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Blood and lymphatic system disorders** | | | |
| Anaemia | | | |
| subjects affected / exposed | 4 / 111 (3.60%) | 2 / 236 (0.85%) | |
| occurrences causally related to treatment / all | 2 / 5 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 2 / 236 (0.85%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| **Ear and labyrinth disorders** | | | |

| | | | |
|---|---|---|---|
| Vertigo | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Eye disorders | | | |
| Blindness unilateral | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Visual acuity reduced | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 3 / 111 (2.70%) | 2 / 236 (0.85%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ascites | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 111 (2.70%) | 2 / 236 (0.85%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Dysphagia | | | |
| subjects affected / exposed | 3 / 111 (2.70%) | 3 / 236 (1.27%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |

| | | | |
|---|---|---|---|
| Gastric disorder | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestinal obstruction | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestine perforation | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal stenosis | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Parotid gland haemorrhage | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumoperitoneum | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tongue haemorrhage | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 2 / 236 (0.85%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Bile duct stenosis | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| 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 | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dermatomyositis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin toxicity | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin mass | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin ulcer | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Endocrine disorders | | | |
| Hypophysitis | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypothyroidism | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Secondary adrenocortical insufficiency | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Secondary hypothyroidism | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Fistula | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Back pain | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pathological fracture | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| 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 | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Device related infection | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal infection | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 2 / 236 (0.85%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Localised infection | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 3 / 111 (2.70%) | 3 / 236 (1.27%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Lymphangitis | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteomyelitis | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Otitis media | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumocystis jirovecii pneumonia | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 5 / 111 (4.50%) | 17 / 236 (7.20%) | |
| occurrences causally related to treatment / all | 2 / 5 | 0 / 21 | |
| deaths causally related to treatment / all | 2 / 2 | 0 / 3 | |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia pseudomonal | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Purulent discharge | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 5 / 236 (2.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 4 / 111 (3.60%) | 6 / 236 (2.54%) | |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 3 / 236 (1.27%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin infection | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Systemic infection | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tracheitis | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 4 / 236 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Vascular device infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound infection | | | |
| subjects affected / exposed | 2 / 111 (1.80%) | 3 / 236 (1.27%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 4 / 236 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 4 / 236 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Electrolyte imbalance | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Failure to thrive | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperamylasaemia | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypernatraemia | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 3 / 236 (1.27%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 4 / 236 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypophagia | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malnutrition | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 3 / 236 (1.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 236 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Investigators Choice | Nivolumab 3mg/kg | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 108 / 111 (97.30%) | 210 / 236 (88.98%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour pain | | | |
| subjects affected / exposed | 8 / 111 (7.21%) | 13 / 236 (5.51%) | |
| occurrences (all) | 10 | 16 | |
| Vascular disorders | | | |

| | | | |
|---|---|---|---|
| Hypertension | | | |
| subjects affected / exposed | 4 / 111 (3.60%) | 16 / 236 (6.78%) | |
| occurrences (all) | 5 | 27 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 24 / 111 (21.62%) | 27 / 236 (11.44%) | |
| occurrences (all) | 32 | 32 | |
| Face oedema | | | |
| subjects affected / exposed | 8 / 111 (7.21%) | 11 / 236 (4.66%) | |
| occurrences (all) | 10 | 11 | |
| Fatigue | | | |
| subjects affected / exposed | 37 / 111 (33.33%) | 67 / 236 (28.39%) | |
| occurrences (all) | 43 | 73 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 19 / 111 (17.12%) | 11 / 236 (4.66%) | |
| occurrences (all) | 24 | 11 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 5 / 111 (4.50%) | 19 / 236 (8.05%) | |
| occurrences (all) | 6 | 26 | |
| Pyrexia | | | |
| subjects affected / exposed | 16 / 111 (14.41%) | 37 / 236 (15.68%) | |
| occurrences (all) | 23 | 46 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 12 / 111 (10.81%) | 32 / 236 (13.56%) | |
| occurrences (all) | 14 | 36 | |
| Cough | | | |
| subjects affected / exposed | 13 / 111 (11.71%) | 37 / 236 (15.68%) | |
| occurrences (all) | 16 | 47 | |
| Epistaxis | | | |
| subjects affected / exposed | 11 / 111 (9.91%) | 5 / 236 (2.12%) | |
| occurrences (all) | 11 | 7 | |
| Pleural effusion | | | |
| subjects affected / exposed | 6 / 111 (5.41%) | 5 / 236 (2.12%) | |
| occurrences (all) | 7 | 5 | |
| Productive cough | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 111 (1.80%) | 14 / 236 (5.93%) | |
| occurrences (all) | 2 | 15 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 9 / 111 (8.11%) | 9 / 236 (3.81%) | |
| occurrences (all) | 9 | 9 | |
| Insomnia | | | |
| subjects affected / exposed | 7 / 111 (6.31%) | 13 / 236 (5.51%) | |
| occurrences (all) | 7 | 13 | |
| Depression | | | |
| subjects affected / exposed | 3 / 111 (2.70%) | 12 / 236 (5.08%) | |
| occurrences (all) | 3 | 13 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 6 / 111 (5.41%) | 9 / 236 (3.81%) | |
| occurrences (all) | 9 | 9 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 6 / 111 (5.41%) | 14 / 236 (5.93%) | |
| occurrences (all) | 9 | 17 | |
| Lipase increased | | | |
| subjects affected / exposed | 2 / 111 (1.80%) | 13 / 236 (5.51%) | |
| occurrences (all) | 2 | 20 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 3 / 111 (2.70%) | 18 / 236 (7.63%) | |
| occurrences (all) | 3 | 20 | |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 6 / 111 (5.41%) | 8 / 236 (3.39%) | |
| occurrences (all) | 7 | 20 | |
| Weight decreased | | | |
| subjects affected / exposed | 19 / 111 (17.12%) | 35 / 236 (14.83%) | |
| occurrences (all) | 22 | 38 | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 8 / 111 (7.21%) | 3 / 236 (1.27%) | |
| occurrences (all) | 11 | 3 | |
| Cardiac disorders | | | |

| | | | |
|---|---|---|---|
| Tachycardia | | | |
| subjects affected / exposed | 7 / 111 (6.31%) | 7 / 236 (2.97%) | |
| occurrences (all) | 7 | 7 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 7 / 111 (6.31%) | 9 / 236 (3.81%) | |
| occurrences (all) | 9 | 12 | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 9 / 111 (8.11%) | 6 / 236 (2.54%) | |
| occurrences (all) | 9 | 6 | |
| Headache | | | |
| subjects affected / exposed | 4 / 111 (3.60%) | 23 / 236 (9.75%) | |
| occurrences (all) | 5 | 35 | |
| Paraesthesia | | | |
| subjects affected / exposed | 6 / 111 (5.41%) | 4 / 236 (1.69%) | |
| occurrences (all) | 6 | 4 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 42 / 111 (37.84%) | 53 / 236 (22.46%) | |
| occurrences (all) | 52 | 63 | |
| Neutropenia | | | |
| subjects affected / exposed | 9 / 111 (8.11%) | 2 / 236 (0.85%) | |
| occurrences (all) | 18 | 2 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 6 / 111 (5.41%) | 4 / 236 (1.69%) | |
| occurrences (all) | 9 | 5 | |
| Eye disorders | | | |
| Lacrimation increased | | | |
| subjects affected / exposed | 6 / 111 (5.41%) | 1 / 236 (0.42%) | |
| occurrences (all) | 6 | 1 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 27 / 111 (24.32%) | 47 / 236 (19.92%) | |
| occurrences (all) | 40 | 65 | |
| Constipation | | | |
| subjects affected / exposed | 21 / 111 (18.92%) | 43 / 236 (18.22%) | |
| occurrences (all) | 23 | 48 | |

| | | | |
|---|---|---|---|
| Dry mouth | | | |
| subjects affected / exposed | 8 / 111 (7.21%) | 8 / 236 (3.39%) | |
| occurrences (all) | 8 | 9 | |
| Dysphagia | | | |
| subjects affected / exposed | 17 / 111 (15.32%) | 30 / 236 (12.71%) | |
| occurrences (all) | 18 | 32 | |
| Dyspepsia | | | |
| subjects affected / exposed | 6 / 111 (5.41%) | 7 / 236 (2.97%) | |
| occurrences (all) | 7 | 9 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 8 / 111 (7.21%) | 3 / 236 (1.27%) | |
| occurrences (all) | 8 | 3 | |
| Stomatitis | | | |
| subjects affected / exposed | 12 / 111 (10.81%) | 14 / 236 (5.93%) | |
| occurrences (all) | 18 | 16 | |
| Nausea | | | |
| subjects affected / exposed | 37 / 111 (33.33%) | 55 / 236 (23.31%) | |
| occurrences (all) | 53 | 75 | |
| Vomiting | | | |
| subjects affected / exposed | 16 / 111 (14.41%) | 28 / 236 (11.86%) | |
| occurrences (all) | 23 | 43 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 16 / 111 (14.41%) | 4 / 236 (1.69%) | |
| occurrences (all) | 16 | 4 | |
| Erythema | | | |
| subjects affected / exposed | 6 / 111 (5.41%) | 3 / 236 (1.27%) | |
| occurrences (all) | 6 | 3 | |
| Dry skin | | | |
| subjects affected / exposed | 12 / 111 (10.81%) | 14 / 236 (5.93%) | |
| occurrences (all) | 12 | 14 | |
| Pruritus | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | 23 / 236 (9.75%) | |
| occurrences (all) | 1 | 24 | |
| Rash | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 6 / 111 (5.41%) | 22 / 236 (9.32%) | |
| occurrences (all) | 7 | 29 | |
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 7 / 111 (6.31%) | 21 / 236 (8.90%) | |
| occurrences (all) | 10 | 22 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 2 / 111 (1.80%) | 19 / 236 (8.05%) | |
| occurrences (all) | 2 | 22 | |
| Back pain | | | |
| subjects affected / exposed | 0 / 111 (0.00%) | 17 / 236 (7.20%) | |
| occurrences (all) | 0 | 17 | |
| Neck pain | | | |
| subjects affected / exposed | 9 / 111 (8.11%) | 17 / 236 (7.20%) | |
| occurrences (all) | 9 | 18 | |
| Infections and infestations | | | |
| Oral candidiasis | | | |
| subjects affected / exposed | 6 / 111 (5.41%) | 11 / 236 (4.66%) | |
| occurrences (all) | 6 | 11 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 6 / 111 (5.41%) | 6 / 236 (2.54%) | |
| occurrences (all) | 7 | 8 | |
| Pneumonia | | | |
| subjects affected / exposed | 5 / 111 (4.50%) | 16 / 236 (6.78%) | |
| occurrences (all) | 5 | 16 | |
| Metabolism and nutrition disorders | | | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 8 / 111 (7.21%) | 17 / 236 (7.20%) | |
| occurrences (all) | 8 | 23 | |
| Decreased appetite | | | |
| subjects affected / exposed | 21 / 111 (18.92%) | 46 / 236 (19.49%) | |
| occurrences (all) | 23 | 54 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 9 / 111 (8.11%) | 16 / 236 (6.78%) | |
| occurrences (all) | 9 | 36 | |

| | | | |
|---|---|---|---|
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 4 / 111 (3.60%) | 12 / 236 (5.08%) | |
| occurrences (all) | 4 | 16 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 7 / 111 (6.31%) | 11 / 236 (4.66%) | |
| occurrences (all) | 9 | 12 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 15 / 111 (13.51%) | 25 / 236 (10.59%) | |
| occurrences (all) | 19 | 28 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 10 July 2014 | Update to investigational product description |
| 30 January 2015 | Update to Endpoints |
| 09 June 2015 | Update to OS interim analysis trigger |
| 11 February 2016 | Update to Study Design |
| 03 November 2016 | Update to the treatment management algorithms and study treatment dose options |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported