# Clinical trial results:
# An Open-label Phase 2 Multi-cohort Trial of Nivolumab in Advanced or Metastatic Malignancies (CheckMate 627: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 627)

## Summary

| | |
|---|---|
| EudraCT number | 2016-000461-23 |
| Trial protocol | DE |
| Global end of trial date | 24 June 2021 |

### Results information

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

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | CA209-627 |

### 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 | 20 August 2021 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 24 June 2021 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the investigator-assessed ORR of nivolumab monotherapy in advanced or metastatic malignancies

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 | 22 February 2016 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Germany: 65 |
| Country: Number of subjects enrolled | United States: 174 |
| Worldwide total number of subjects | 239 |
| EEA total number of subjects | 65 |

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) | 152 |
| From 65 to 84 years | 84 |
| 85 years and over | 3 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

239 participants were treated.

### Period 1

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

### Arms

| | |
|---|---|
| **Arm title** | Advanced Malignancies Cohort |

Arm description:

Treatment period 1: Nivolumab 240 mg Q2W for 8 doses. Treatment period 2: Nivolumab 480 mg Q4W

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | BMS-936558 |
| Investigational medicinal product code | |
| Other name | Nivolumab |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

240 mg Q2W for 8 doses

| **Number of subjects in period 1** | Advanced Malignancies Cohort |
|---|---|
| Started | 239 |
| Completed | 110 |
| Not completed | 129 |
| Adverse event, serious fatal | 2 |
| No longer meet study criteria | 1 |
| Disease progression | 90 |
| Participant withdrew consent | 3 |
| Participant request to discontinue | 9 |
| Adverse event unrelated to study drug | 12 |
| Other reasons | 6 |
| Study Drug Toxicity | 6 |

## Period 2

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

## Arms

| | |
|---|---|
| **Arm title** | Advanced Malignancies Cohort |

Arm description:

Treatment period 1: Nivolumab 240 mg Q2W for 8 doses. Treatment period 2: Nivolumab 480 mg Q4W

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | BMS-936558 |
| Investigational medicinal product code | |
| Other name | Nivolumab |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

480 mg Q4W up to 24 months of total treatment (Treatment Period 1 + Treatment Period 2)

| **Number of subjects in period 2[1]** | Advanced Malignancies Cohort |
|---|---|
| Started | 103 |
| Completed | 19 |
| Not completed | 84 |
| Disease progression | 69 |
| Participant withdrew consent | 3 |
| Maximum clinical benefit | 1 |
| Participant request to discontinue | 2 |
| Adverse event unrelated to study drug | 1 |
| Other reasons | 3 |
| Study Drug Toxicity | 5 |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Not all the participants who completed Treatment Period 1 continued in Treatment Period 2

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Advanced Malignancies Cohort |
| Reporting group description: | |
| Treatment period 1: Nivolumab 240 mg Q2W for 8 doses. Treatment period 2: Nivolumab 480 mg Q4W | |

| Reporting group values | Advanced Malignancies Cohort | Total | |
|---|---|---|---|
| Number of subjects | 239 | 239 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 152 | 152 | |
| From 65-84 years | 84 | 84 | |
| 85 years and over | 3 | 3 | |
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | 59.2 | | |
| standard deviation | ± 13.79 | - | |
| Sex: Female, Male<br>Units: Participants | | | |
| Female | 148 | 148 | |
| Male | 91 | 91 | |
| Race (NIH/OMB)<br>Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | |
| Asian | 9 | 9 | |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | |
| Black or African American | 20 | 20 | |
| White | 203 | 203 | |
| More than one race | 0 | 0 | |
| Unknown or Not Reported | 7 | 7 | |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 11 | 11 | |
| Not Hispanic or Latino | 158 | 158 | |
| Unknown or Not Reported | 70 | 70 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Advanced Malignancies Cohort |
| Reporting group description: | |
| Treatment period 1: Nivolumab 240 mg Q2W for 8 doses. Treatment period 2: Nivolumab 480 mg Q4W | |
| Reporting group title | Advanced Malignancies Cohort |
| Reporting group description: | |
| Treatment period 1: Nivolumab 240 mg Q2W for 8 doses. Treatment period 2: Nivolumab 480 mg Q4W | |

### Primary: Objective Response Rate (ORR)

| | |
|---|---|
| End point title | Objective Response Rate (ORR)[1] |

End point description:

ORR is defined as the percentage of participants with a best overall response (BOR) of confirmed Complete Response (CR) or Partial Response (PR). Best overall response is defined as the best response designation, as determined by investigator, recorded in the specified timeframe, according to the RECIST 1.1 criteria.

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

End point timeframe:

From first dose to the date of objectively documented progression (per tumor-specific response criteria) or the date of subsequent therapy, whichever occurs first (up to approximately 24 months)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were performed for this endpoint

| End point values | Advanced Malignancies Cohort | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 239 | | | |
| Units: Percent of Participants | | | | |
| number (confidence interval 95%) | 7.9 (4.9 to 12.1) | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of Response (DOR)

| | |
|---|---|
| End point title | Duration of Response (DOR) |

End point description:

DOR is defined as the time from first confirmed response (Complete Response, CR or Partial Response, PR) to the date of the first documented tumor progression (as determined by investigator) or death due to any cause, whichever occurs first. Median DOR computed using Kaplan-Meier method

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

End point timeframe:

From the time of first confirmed response to the date of the first documented progression (up to approximately 22 months)

| End point values | Advanced Malignancies Cohort | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 19 | | | |
| Units: Months | | | | |
| median (full range (min-max)) | 21.78 (2.8 to 22.3) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Objective Response (TTR)

| End point title | Time to Objective Response (TTR) |
|---|---|

End point description:

TTR is defined as the time from first dosing date to the date of the first confirmed response (Complete Response, CR or Partial Response, PR), as assessed by investigator.

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

End point timeframe:

From the first dosing date to the date of the first confirmed response (up to approximately 10 months)

| End point values | Advanced Malignancies Cohort | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 19 | | | |
| Units: Months | | | | |
| arithmetic mean (standard deviation) | 3.54 (± 2.337) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Clinical Benefit Rate (CBR)

| End point title | Clinical Benefit Rate (CBR) |
|---|---|

End point description:

CBR is defined as the percentage of participants with a best overall response of confirmed Complete Response (CR) or Partial Response (PR) or Stable Disease (SD).

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

End point timeframe:

From the first dosing date to the date of the last dose (approximately 24 months)

| End point values | Advanced Malignancies Cohort | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 239 | | | |
| Units: Percent of participants | | | | |
| number (confidence interval 95%) | 49.8 (43.3 to 56.3) | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Survival Rate at 1 Year

| End point title | Overall Survival Rate at 1 Year |
|---|---|

End point description:

Overall Survival (OS) is defined as the time from the first dosing date to the date of death. A participant who has not died will be censored at last known date alive. OS rate at 1 year is measured as the percent of participants still alive at 1 year after first dosing, measured from Kaplan-Meier curve of OS.

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

End point timeframe:

From the first dosing date to 1 year later

| End point values | Advanced Malignancies Cohort | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 239 | | | |
| Units: Percent of participants | | | | |
| number (confidence interval 95%) | 56.1 (49.1 to 62.5) | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants Who Died

| End point title | Number of Participants Who Died |
|---|---|

End point description:

Number of participants who died for any cause

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

End point timeframe:

From first dose to 100 days following last dose (up approximately 27 months)

| **End point values** | Advanced Malignancies Cohort | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 239 | | | |
| Units: Participants | 72 | | | |

### Statistical analyses

No statistical analyses for this end point

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

| End point title | Number of Participants Experiencing Adverse Events (AEs) |
|---|---|

End point description:

Number of participants who experienced any grade, any cause AEs

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

End point timeframe:

From first dose to 30 days following the last dose (up to approximately 25 months)

| **End point values** | Advanced Malignancies Cohort | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 239 | | | |
| Units: Participants | 234 | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants Experiencing Serious Adverse Events (SAEs)

| End point title | Number of Participants Experiencing Serious Adverse Events (SAEs) |
|---|---|

End point description:

Number of participants who experienced any grade, any cause SAEs

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

End point timeframe:

From first dose to 100 days following the last dose (up to approximately 27 months)

| End point values | Advanced Malignancies Cohort | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 239 | | | |
| Units: Participants | 148 | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants Experiencing Adverse Events (AEs) Leading to Discontinuation

| End point title | Number of Participants Experiencing Adverse Events (AEs) Leading to Discontinuation |
|---|---|

End point description:

Number of participants who experienced AEs leading to discontinuation of study therapy

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

End point timeframe:

From first dose to 30 days following the last dose (up to approximately 25 months)

| End point values | Advanced Malignancies Cohort | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 239 | | | |
| Units: Participants | 41 | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants Experiencing Immune-mediated Adverse Events (IMAEs)

| End point title | Number of Participants Experiencing Immune-mediated Adverse Events (IMAEs) |
|---|---|

End point description:

Number of participants who experienced IMAEs. IMAEs are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. IMAEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity.

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

End point timeframe:

From first dose to 100 days following the last dose (up to approximately 27 months)

| **End point values** | Advanced Malignancies Cohort | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 239 | | | |
| Units: Participants | 8 | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants Experiencing Select Adverse Events

| End point title | Number of Participants Experiencing Select Adverse Events |
|---|---|

End point description:

Number of participants who experienced Select Adverse Events. Select Adverse Events categories include: gastrointestinal, hepatic, pulmonary, renal, skin, hypersensitivity/infusion reaction.

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

End point timeframe:

From first dose to 30 days following the last dose (up to approximately 25 months)

| **End point values** | Advanced Malignancies Cohort | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 239 | | | |
| Units: Participants | | | | |
| Gastrointestinal Select AEs | 57 | | | |
| Hepatic Select AEs | 33 | | | |
| Pulmonary Select AEs | 6 | | | |
| Renal Select AEs | 22 | | | |
| Skin Select AEs | 59 | | | |
| Hypersensitivity/Infusion Reaction | 7 | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants Experiencing Adverse Events (AEs) Leading to Dose Delay or Dose Reduction

| End point title | Number of Participants Experiencing Adverse Events (AEs) |
|---|---|

| | |
|---|---|
| | Leading to Dose Delay or Dose Reduction |

End point description:

Number of participants who experienced AEs leading to dose delay or dose reduction. A dose will be considered as delayed if the delay is exceeding 3 days after the intended dose date (i.e., greater than or equal to 4 days from scheduled dosing date)

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

End point timeframe:

From first dose to 30 days following the last dose (up to approximately 25 months)

| **End point values** | Advanced Malignancies Cohort | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 239 | | | |
| Units: Participants | 61 | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants Experiencing Laboratory Abnormalities in Specific Liver Tests

| | |
|---|---|
| End point title | Number of Participants Experiencing Laboratory Abnormalities in Specific Liver Tests |

End point description:

Number of participants who experienced the laboratory abnormalities in specific liver tests described in the individual categories. ALT = Alanine Aminotransferase AST = Aspartate Aminotransferase ULN = Upper Limit of Normal

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

End point timeframe:

From first dose to 30 days following the last dose (up to approximately 25 months)

| **End point values** | Advanced Malignancies Cohort | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 231 | | | |
| Units: Participants | | | | |
| ALT OR AST > 3XULN | 11 | | | |
| ALT OR AST > 5XULN | 8 | | | |
| ALT OR AST > 10XULN | 3 | | | |
| ALT OR AST > 20XULN | 1 | | | |
| TOTAL BILIRUBIN > 2XULN | 5 | | | |
| ALT/AST > 3XULN + BILIR > 2XULN 1 DAY | 3 | | | |
| ALT/AST > 3XULN + BILIR > 2XULN 30 DAYS | 3 | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants Experiencing Laboratory Abnormalities in Specific Thyroid Tests

| End point title | Number of Participants Experiencing Laboratory Abnormalities in Specific Thyroid Tests |
|---|---|

End point description:

Number of participants who experienced the laboratory abnormalities in specific thyroid tests described in the individual categories. TSH = Thyroid Stimulating Hormone LLN = Lower Limit of Normal ULN = Upper Limit of Normal

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

End point timeframe:

From first dose to 100 days following the last dose (up to approximately 27 months)

| End point values | Advanced Malignancies Cohort | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 238 | | | |
| Units: Participants | | | | |
| TSH > ULN | 62 | | | |
| TSH > ULN WITH TSH <= ULN AT BASELINE | 42 | | | |
| TSH > ULN WITH AT LEAST 1 FT3/FT4 TEST VALUE < LLN | 12 | | | |
| TSH > ULN WITH ALL FT3/FT4 TEST VALUE >= LLN | 0 | | | |
| TSH > ULN WITH FT3/FT4 MISSING | 2 | | | |
| TSH < LLN | 38 | | | |
| TSH < LLN WITH TSH >= LLN AT BASELINE | 25 | | | |
| TSH < LLN WITH AT LEAST 1 FT3/FT4 TEST VALUE > ULN | 8 | | | |
| TSH < LLN WITH ALL FT3/FT4 TEST VALUES <= ULN | 1 | | | |
| TSH < LLN WITH FT3/FT4 TEST MISSING | 1 | | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All-cause mortality was assessed from first dose to study completion date (approximately 64 months). SAEs and Other AEs were assessed from first dose to 100 days following administration of the last dose (approximately 27 months).

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

### Dictionary used

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

### Reporting groups

| | |
|---|---|
| Reporting group title | Advanced Malignancies Cohort |

Reporting group description:

Treatment period 1: Nivolumab 240 mg Q2W for 8 doses. Treatment period 2: Nivolumab 480 mg Q4W

| Serious adverse events | Advanced Malignancies Cohort | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 148 / 239 (61.92%) | | |
| number of deaths (all causes) | 156 | | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Infected neoplasm | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Brain neoplasm | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Adenoid cystic carcinoma | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Malignant neoplasm of cornea | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Malignant neoplasm progression | | | | |
| subjects affected / exposed | 58 / 239 (24.27%) | | | |
| occurrences causally related to treatment / all | 0 / 59 | | | |
| deaths causally related to treatment / all | 0 / 52 | | | |
| Mesothelioma | | | | |
| subjects affected / exposed | 2 / 239 (0.84%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 2 | | | |
| Tumour haemorrhage | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Tumour pain | | | | |
| subjects affected / exposed | 4 / 239 (1.67%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Squamous cell carcinoma | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Penis carcinoma metastatic | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Neoplasm progression | | | | |
| subjects affected / exposed | 2 / 239 (0.84%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 2 | | | |
| Transitional cell carcinoma | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Embolism | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Venous stenosis | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 4 / 239 (1.67%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Asthenia | | | |
| subjects affected / exposed | 2 / 239 (0.84%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|---|---|---|---|
| Localised oedema | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Peripheral swelling | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Sudden death | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Pyrexia | | | | |
| subjects affected / exposed | 2 / 239 (0.84%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Immune system disorders | | | | |
| Anaphylactic reaction | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Reproductive system and breast disorders | | | | |
| Vaginal haemorrhage | | | | |
| subjects affected / exposed | 2 / 239 (0.84%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Vulvovaginal pain | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Respiratory, thoracic and mediastinal disorders | | | | |
| Acute respiratory failure | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 3 / 239 (1.26%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bronchostenosis | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pleural effusion | | | | |
| subjects affected / exposed | 4 / 239 (1.67%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumothorax | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Laryngeal haemorrhage | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hypoxia | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Dyspnoea | | | | |
| subjects affected / exposed | 5 / 239 (2.09%) | | | |
| occurrences causally related to treatment / all | 0 / 6 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Pulmonary embolism | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pulmonary hypertension | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Mental status changes | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Delirium | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Transaminases increased | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| C-reactive protein increased | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 2 / 239 (0.84%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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|---|---|---|---|---|
| Post procedural fever | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| **Cardiac disorders** | | | | |
| Acute myocardial infarction | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiac arrest | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Cardiac failure congestive | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Cardio-respiratory arrest | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Myocardial infarction | | | | |
| subjects affected / exposed | 2 / 239 (0.84%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Supraventricular tachycardia | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ventricular tachycardia | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| **Nervous system disorders** | | | | |

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|---|---|---|---|---|
| Brain oedema | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cerebellar infarction | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Spinal cord compression | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Neuritis cranial | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intracranial mass | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Headache | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Facial paralysis | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cerebrovascular accident | | | | |
| subjects affected / exposed | 2 / 239 (0.84%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cerebral infarction | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 3 / 239 (1.26%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Eye swelling | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye pain | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 9 / 239 (3.77%) | | |
| occurrences causally related to treatment / all | 0 / 12 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 5 / 239 (2.09%) | | |
| occurrences causally related to treatment / all | 2 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colitis | | | |
| subjects affected / exposed | 4 / 239 (1.67%) | | |
| occurrences causally related to treatment / all | 4 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 2 / 239 (0.84%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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|---|---|---|---|---|
| Abdominal pain lower | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Diverticulum intestinal haemorrhagic | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Dysphagia | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastric haemorrhage | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Gastrointestinal haemorrhage | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lower gastrointestinal haemorrhage | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Inguinal hernia | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ileus | | | | |
| subjects affected / exposed | 2 / 239 (0.84%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal oedema | | | | |

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|---|---|---|---|---|
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intestinal obstruction | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Subileus | | | | |
| subjects affected / exposed | 2 / 239 (0.84%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Small intestinal obstruction | | | | |
| subjects affected / exposed | 6 / 239 (2.51%) | | | |
| occurrences causally related to treatment / all | 1 / 7 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Proctalgia | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Nausea | | | | |
| subjects affected / exposed | 4 / 239 (1.67%) | | | |
| occurrences causally related to treatment / all | 2 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Vomiting | | | | |
| subjects affected / exposed | 4 / 239 (1.67%) | | | |
| occurrences causally related to treatment / all | 1 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hepatobiliary disorders | | | | |
| Cholecystitis | | | | |
| subjects affected / exposed | 3 / 239 (1.26%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hepatic lesion | | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 4 / 239 (1.67%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Chronic kidney disease | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hydronephrosis | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal failure | | | |
| subjects affected / exposed | 2 / 239 (0.84%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Urinary tract obstruction | | | |
| subjects affected / exposed | 2 / 239 (0.84%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocrine disorders | | | |

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|---|---|---|---|
| Hypophysitis | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperthyroidism | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| **Musculoskeletal and connective tissue disorders** | | | |
| Flank pain | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Back pain | | | |
| subjects affected / exposed | 3 / 239 (1.26%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Arthralgia | | | |
| subjects affected / exposed | 2 / 239 (0.84%) | | |
| occurrences causally related to treatment / all | 2 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neck pain | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myositis | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |

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|---|---|---|---|
| Infections and infestations | | | |
| Bacteraemia | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholecystitis infective | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cellulitis | | | |
| subjects affected / exposed | 3 / 239 (1.26%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Device related infection | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Febrile infection | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Erysipelas | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Enterocolitis infectious | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diverticulitis | | | |

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|---|---|---|---|---|
| subjects affected / exposed | 2 / 239 (0.84%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Diarrhoea infectious | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Fungaemia | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastroenteritis | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Herpes zoster | | | | |
| subjects affected / exposed | 2 / 239 (0.84%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pelvic abscess | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Pneumonia | | | | |
| subjects affected / exposed | 7 / 239 (2.93%) | | | |
| occurrences causally related to treatment / all | 0 / 8 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pharyngitis streptococcal | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intervertebral discitis | | | | |

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|---|---|---|---|---|
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infectious pleural effusion | | | | |
| subjects affected / exposed | 2 / 239 (0.84%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Perinephric abscess | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Renal abscess | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Sepsis | | | | |
| subjects affected / exposed | 8 / 239 (3.35%) | | | |
| occurrences causally related to treatment / all | 0 / 10 | | | |
| deaths causally related to treatment / all | 0 / 3 | | | |
| Septic shock | | | | |
| subjects affected / exposed | 2 / 239 (0.84%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Skin infection | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Urinary tract infection | | | | |
| subjects affected / exposed | 3 / 239 (1.26%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Urosepsis | | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypovolaemia | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dehydration | | | |
| subjects affected / exposed | 5 / 239 (2.09%) | | |
| occurrences causally related to treatment / all | 2 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lactic acidosis | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| **Non-serious adverse events** | Advanced Malignancies Cohort | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 216 / 239 (90.38%) | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 17 / 239 (7.11%) | | |
| occurrences (all) | 17 | | |
| General disorders and administration site conditions | | | |
| Chills | | | |
| subjects affected / exposed | 14 / 239 (5.86%) | | |
| occurrences (all) | 16 | | |
| Fatigue | | | |
| subjects affected / exposed | 90 / 239 (37.66%) | | |
| occurrences (all) | 102 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 24 / 239 (10.04%) | | |
| occurrences (all) | 25 | | |
| Pyrexia | | | |
| subjects affected / exposed | 24 / 239 (10.04%) | | |
| occurrences (all) | 29 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 43 / 239 (17.99%) | | |
| occurrences (all) | 53 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 44 / 239 (18.41%) | | |
| occurrences (all) | 51 | | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 18 / 239 (7.53%) | | |
| occurrences (all) | 18 | | |
| Anxiety | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 13 / 239 (5.44%) | | |
| occurrences (all) | 13 | | |
| Investigations | | | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 12 / 239 (5.02%) | | |
| occurrences (all) | 12 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 18 / 239 (7.53%) | | |
| occurrences (all) | 19 | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 16 / 239 (6.69%) | | |
| occurrences (all) | 19 | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 15 / 239 (6.28%) | | |
| occurrences (all) | 15 | | |
| Weight decreased | | | |
| subjects affected / exposed | 22 / 239 (9.21%) | | |
| occurrences (all) | 23 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 19 / 239 (7.95%) | | |
| occurrences (all) | 21 | | |
| Dizziness | | | |
| subjects affected / exposed | 15 / 239 (6.28%) | | |
| occurrences (all) | 15 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 41 / 239 (17.15%) | | |
| occurrences (all) | 42 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 33 / 239 (13.81%) | | |
| occurrences (all) | 35 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 12 / 239 (5.02%) | | |
| occurrences (all) | 12 | | |

| | | | |
|---|---|---|---|
| Vomiting<br>subjects affected / exposed<br>occurrences (all) | 32 / 239 (13.39%)<br>39 | | |
| Nausea<br>subjects affected / exposed<br>occurrences (all) | 53 / 239 (22.18%)<br>65 | | |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all) | 52 / 239 (21.76%)<br>66 | | |
| Constipation<br>subjects affected / exposed<br>occurrences (all) | 50 / 239 (20.92%)<br>50 | | |
| Dry mouth<br>subjects affected / exposed<br>occurrences (all) | 14 / 239 (5.86%)<br>14 | | |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus<br>subjects affected / exposed<br>occurrences (all) | 26 / 239 (10.88%)<br>29 | | |
| Rash<br>subjects affected / exposed<br>occurrences (all) | 20 / 239 (8.37%)<br>21 | | |
| Dry skin<br>subjects affected / exposed<br>occurrences (all) | 12 / 239 (5.02%)<br>12 | | |
| Endocrine disorders | | | |
| Hypothyroidism<br>subjects affected / exposed<br>occurrences (all) | 21 / 239 (8.79%)<br>22 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all) | 15 / 239 (6.28%)<br>16 | | |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 34 / 239 (14.23%)<br>38 | | |

| | | | |
|---|---|---|---|
| Back pain | | | |
| subjects affected / exposed | 27 / 239 (11.30%) | | |
| occurrences (all) | 30 | | |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 22 / 239 (9.21%) | | |
| occurrences (all) | 26 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 17 / 239 (7.11%) | | |
| occurrences (all) | 21 | | |
| Metabolism and nutrition disorders | | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 18 / 239 (7.53%) | | |
| occurrences (all) | 24 | | |
| Dehydration | | | |
| subjects affected / exposed | 23 / 239 (9.62%) | | |
| occurrences (all) | 28 | | |
| Decreased appetite | | | |
| subjects affected / exposed | 37 / 239 (15.48%) | | |
| occurrences (all) | 39 | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 15 / 239 (6.28%) | | |
| occurrences (all) | 17 | | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 12 / 239 (5.02%) | | |
| occurrences (all) | 14 | | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 12 January 2018 | - Changes to primary endpoint - Statistical section updates - Adverse events updates |
| 31 May 2018 | Statistical section updates |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported