# Clinical trial results:
# A Phase II Single-arm, Open-label Monotherapy Clinical Trial of Pembrolizumab (MK-3475) in Locally Advanced/Metastatic Renal Cell Carcinoma (mRCC) (KEYNOTE-427)

## Summary

| | |
|---|---|
| EudraCT number | 2016-000589-47 |
| Trial protocol | DE DK GB ES CZ PL |
| Global end of trial date | 01 April 2022 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 06 April 2023 |
| First version publication date | 06 April 2023 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | 3475-427 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02853344 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Merck Sharp & Dohme LLC |
| Sponsor organisation address | 126 East Lincoln Avenue, P.O. Box 2000, Rahway, NJ, United States, 07065 |
| Public contact | Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.com |
| Scientific contact | Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.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 | 01 April 2022 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 05 February 2021 |
| Global end of trial reached? | Yes |
| Global end of trial date | 01 April 2022 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The purpose of this study is to assess the safety and efficacy of monotherapy pembrolizumab (MK-3475) in participants with renal cell carcinoma (RCC). There will be two cohorts in this study: Cohort A will consist of participants with clear cell (cc) RCC and Cohort B will consist of participants with non-clear cell (ncc) RCC.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 30 September 2016 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 63 Months |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Canada: 28 |
| Country: Number of subjects enrolled | Czechia: 13 |
| Country: Number of subjects enrolled | Denmark: 26 |
| Country: Number of subjects enrolled | Germany: 6 |
| Country: Number of subjects enrolled | Korea, Republic of: 23 |
| Country: Number of subjects enrolled | Poland: 42 |
| Country: Number of subjects enrolled | Russian Federation: 27 |
| Country: Number of subjects enrolled | Spain: 24 |
| Country: Number of subjects enrolled | United Kingdom: 27 |
| Country: Number of subjects enrolled | United States: 59 |
| Worldwide total number of subjects | 275 |
| EEA total number of subjects | 111 |

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) | 164 |
| From 65 to 84 years | 107 |
| 85 years and over | 4 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Participants who met the following key criteria at screening were eligible for enrollment:
1. Histologically confirmed diagnosis of ccRCC or nccRCC.
2. Had locally advanced/metastatic disease.
3. Had measurable disease per RECIST 1.1 as assessed by BICR.
4. Had received no prior systemic therapy for advanced RCC.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Cohort A: Clear Cell RCC |

Arm description:

Participants with clear cell RCC received pembrolizumab 200 mg intravenously (IV) every 3 weeks (Q3W) for up to 35 doses (approximately 24 months).

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Pembrolizumab |
| Investigational medicinal product code | |
| Other name | MK-3475<br>Keytruda |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

200 mg intravenously (IV) every 3 weeks (Q3W)

| | |
|---|---|
| **Arm title** | Cohort B: Non-clear Cell RCC |

Arm description:

Participants with non-clear cell RCC received pembrolizumab 200 mg IV Q3W for up to 35 doses (approximately 24 months).

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Pembrolizumab |
| Investigational medicinal product code | |
| Other name | MK-3475<br>Keytruda |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

200 mg intravenously (IV) every 3 weeks (Q3W)

| **Number of subjects in period 1** | Cohort A: Clear Cell RCC | Cohort B: Non-clear Cell RCC |
|---|---|---|
| Started | 110 | 165 |
| Received Second Course of Pembrolizumab | 3 | 5 |
| Completed | 0 | 0 |
| Not completed | 110 | 165 |
| Consent withdrawn by subject | 2 | 4 |
| Death | 70 | 112 |
| Participation in Study Terminated by Sponsor | 37 | 48 |
| Lost to follow-up | 1 | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Cohort A: Clear Cell RCC |
| Reporting group description: | |
| Participants with clear cell RCC received pembrolizumab 200 mg intravenously (IV) every 3 weeks (Q3W) for up to 35 doses (approximately 24 months). | |
| Reporting group title | Cohort B: Non-clear Cell RCC |
| Reporting group description: | |
| Participants with non-clear cell RCC received pembrolizumab 200 mg IV Q3W for up to 35 doses (approximately 24 months). | |

| Reporting group values | Cohort A: Clear Cell RCC | Cohort B: Non-clear Cell RCC | Total |
|---|---|---|---|
| Number of subjects | 110 | 165 | 275 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 58 | 106 | 164 |
| From 65-84 years | 49 | 58 | 107 |
| 85 years and over | 3 | 1 | 4 |
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | 62.9 | 60.0 | |
| standard deviation | ± 11.0 | ± 12.3 | - |
| Sex: Female, Male<br>Units: Participants | | | |
| Female | 24 | 56 | 80 |
| Male | 86 | 109 | 195 |
| Race (NIH/OMB)<br>Units: Subjects | | | |
| American Indian or Alaska Native | 1 | 1 | 2 |
| Asian | 11 | 17 | 28 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 0 | 1 | 1 |
| White | 98 | 145 | 243 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 0 | 1 | 1 |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 2 | 1 | 3 |
| Not Hispanic or Latino | 104 | 156 | 260 |
| Unknown or Not Reported | 4 | 8 | 12 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Cohort A: Clear Cell RCC |
| Reporting group description: | |
| Participants with clear cell RCC received pembrolizumab 200 mg intravenously (IV) every 3 weeks (Q3W) for up to 35 doses (approximately 24 months). | |
| Reporting group title | Cohort B: Non-clear Cell RCC |
| Reporting group description: | |
| Participants with non-clear cell RCC received pembrolizumab 200 mg IV Q3W for up to 35 doses (approximately 24 months). | |

### Primary: Objective Response Rate (ORR)

| | |
|---|---|
| End point title | Objective Response Rate (ORR)[1] |
| End point description: | |
| ORR was defined as the percentage of participants who had a Complete Response (CR: Disappearance of all target lesions) or a Partial Response (PR: At least a 30% decrease in the sum of diameters of target lesions) as assessed by Blinded Independent Central Review (BICR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). The population analyzed included all allocated participants who received at least one dose of study treatment. | |
| End point type | Primary |
| End point timeframe: | |
| Up to approximately 66 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 planned for this endpoint.

| End point values | Cohort A: Clear Cell RCC | Cohort B: Non-clear Cell RCC | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 110 | 165 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 36.4 (27.4 to 46.1) | 26.7 (20.1 to 34.1) | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of Response (DOR)

| | |
|---|---|
| End point title | Duration of Response (DOR) |
| End point description: | |
| For participants who demonstrated a confirmed Complete Response (CR: disappearance of all target lesions) or Partial Response (PR: At least a 30% decrease in the sum of diameters of target lesions) per RECIST 1.1, DOR was defined as the time from first documented evidence of a CR or PR until progressive disease (PD) or death. DOR for participants who had not progressed or died at the time of analysis was censored at the date of their last tumor assessment. Per RECIST 1.1, PD was defined as at least a 20% increase in the sum of diameters of target lesions as well as an absolute increase of at least 5 mm in the sum of diameters. The appearance of one or more new lesions was also considered PD. | |

DOR assessments were based on BICR. The DOR as assessed using RECIST 1.1 for all participants who experienced a confirmed CR or PR is presented. The population analyzed included all allocated participants who received at least one dose of study treatment and had confirmed CR or PR.

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

End point timeframe:

Up to approximately 66 months

| **End point values** | Cohort A: Clear Cell RCC | Cohort B: Non-clear Cell RCC | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 110[2] | 165[3] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 18.9 (2.3 to 9999) | 29.0 (2.8 to 9999) | | |

Notes:

[2] - 9999 = upper limit not reached due to insufficient number of responding participants with PD.

[3] - 9999 = upper limit not reached due to insufficient number of responding participants with PD.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Disease Control Rate (DCR)

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

End point description:

DCR is defined as the percentage of participants who have achieved CR, PR, or Stable Disease (SD) for at least 6 months based on assessments by the BICR per RECIST 1.1. CR is defined as disappearance of all target lesions, PR is defined as at least a 30% decrease in the sum of diameters of target lesions, SD is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions and an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered PD. The population analyzed included all allocated participants who received at least one dose of study treatment.

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

End point timeframe:

Up to approximately 66 months

| **End point values** | Cohort A: Clear Cell RCC | Cohort B: Non-clear Cell RCC | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 110 | 165 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 58.2 (48.4 to 67.5) | 43.0 (35.4 to 51.0) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Progression-free Survival (PFS)

| End point title | Progression-free Survival (PFS) |
|---|---|

End point description:

PFS is defined as the time from first dose of study treatment to the first documented progressive disease (PD) per RECIST 1.1 based on BICR, or death due to any cause, whichever occurs first. Per RECIST 1.1, PD is defined as ≥20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of ≥5 mm. The appearance of one or more new lesions is also considered PD. The population analyzed included all allocated participants who received at least one dose of study treatment.

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

End point timeframe:

Up to approximately 66 months

| End point values | Cohort A: Clear Cell RCC | Cohort B: Non-clear Cell RCC | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 110 | 165 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 7.1 (5.6 to 11.0) | 4.2 (2.9 to 5.6) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Overall Survival

| End point title | Overall Survival |
|---|---|

End point description:

OS was defined as the time from first dose of study treatment to death due to any cause. The population analyzed included all allocated participants who received at least one dose of study treatment.

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

End point timeframe:

Up to approximately 66 months

| End point values | Cohort A: Clear Cell RCC | Cohort B: Non-clear Cell RCC | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 110 | 165 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 40.7 (31.1 to 52.6) | 29.9 (24.3 to 37.4) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants Who Experienced an Adverse Event (AE)

| End point title | Number of Participants Who Experienced an Adverse Event (AE) |
|---|---|

End point description:

An adverse event is defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. The population analyzed included all allocated participants who received at least one dose of study treatment.

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

End point timeframe:

Up to approximately 27 months

| End point values | Cohort A: Clear Cell RCC | Cohort B: Non-clear Cell RCC | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 110 | 165 | | |
| Units: Participants | 109 | 155 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants Who Discontinued Study Drug Due to an AE

| End point title | Number of Participants Who Discontinued Study Drug Due to an AE |
|---|---|

End point description:

An adverse event is defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. The population analyzed included all allocated participants who received at least one dose of study treatment.

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

End point timeframe:

Up to approximately 24 months

| End point values | Cohort A: Clear Cell RCC | Cohort B: Non-clear Cell RCC | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 110 | 165 | | |
| Units: Participants | 23 | 25 | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to approximately 66 months

Adverse event reporting additional description:

Safety analysis population includes all participants who received at least one dose of study treatment. Progression of cancer under study was not an AE unless considered related to study treatment. Therefore, MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" unrelated to the drug are excluded.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 24.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Cohort B: nccRCC First Course |

Reporting group description:

Participants with non-clear cell RCC received pembrolizumab 200 mg IV Q3W for up to 35 doses (approximately 24 months)

| | |
|---|---|
| Reporting group title | Cohort B: nccRCC Second Course |

Reporting group description:

Participants with non-clear cell RCC received pembrolizumab 200 mg IV Q3W for up to 35 doses (approximately 24 months). Eligible participants with nccRCC who experienced disease progression received up to 17 additional doses of pembrolizumab.

| | |
|---|---|
| Reporting group title | Cohort A: ccRCC First Course |

Reporting group description:

Participants with clear cell RCC received pembrolizumab 200 mg intravenously (IV) every 3 weeks (Q3W) for up to 35 doses (approximately 24 months).

| | |
|---|---|
| Reporting group title | Cohort A: ccRCC Second Course |

Reporting group description:

Participants with clear cell RCC received pembrolizumab 200 mg IV Q3W for up to 35 doses (approximately 24 months). Eligible participants with ccRCC who experienced disease progression received up to 17 additional doses of pembrolizumab.

| Serious adverse events | Cohort B: nccRCC First Course | Cohort B: nccRCC Second Course | Cohort A: ccRCC First Course |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 47 / 165 (28.48%) | 0 / 5 (0.00%) | 52 / 110 (47.27%) |
| number of deaths (all causes) | 113 | 0 | 71 |
| number of deaths resulting from adverse events | 2 | 0 | 1 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| B-cell small lymphocytic lymphoma | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal cell carcinoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transitional cell carcinoma | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Peripheral artery aneurysm | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotension | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral artery stenosis | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chest pain | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Asthenia | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Pyrexia | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 2 / 110 (1.82%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Stent-graft endoleak | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Contrast media allergy | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 2 / 165 (1.21%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atelectasis | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 3 / 165 (1.82%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 165 (1.21%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 2 / 110 (1.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Delirium | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Product issues | | | |
| Device dislocation | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Acetabulum fracture | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Joint dislocation | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 2 / 110 (1.82%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery disease | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac arrest | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Atrial thrombosis | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Left ventricular failure | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Myocarditis | | | |
| subjects affected / exposed | 2 / 165 (1.21%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericarditis | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Nervous system disorders** | | | |
| Aphasia | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bell's palsy | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral infarction | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 2 / 110 (1.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Encephalopathy | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhagic stroke | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myasthenic syndrome | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lacunar infarction | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neuritis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myelopathy | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal cord compression | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Blood and lymphatic system disorders** | | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lymphadenopathy | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Gastrointestinal disorders** | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 3 / 165 (1.82%) | 0 / 5 (0.00%) | 4 / 110 (3.64%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 4 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 4 / 110 (3.64%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 5 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ileus | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric ulcer | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophageal varices haemorrhage | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Autoimmune hepatitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 165 (1.21%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 2 / 110 (1.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 2 / 110 (1.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatotoxicity | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis cholestatic | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Nephritis | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute kidney injury | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 165 (1.21%) | 0 / 5 (0.00%) | 2 / 110 (1.82%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Secondary adrenocortical insufficiency | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myositis | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pathological fracture | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Polyarthritis | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Abdominal abscess | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal bacterial infection | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalitis | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia sepsis | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 165 (1.21%) | 0 / 5 (0.00%) | 2 / 110 (1.82%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 2 / 110 (1.82%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular device infection | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Adult failure to thrive | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dehydration | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 2 / 110 (1.82%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Type 1 diabetes mellitus | | | |
| subjects affected / exposed | 2 / 165 (1.21%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 2 / 165 (1.21%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 3 / 110 (2.73%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | Cohort A: ccRCC Second Course | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |

| | | | |
|---|---|---|---|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| B-cell small lymphocytic lymphoma | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal cell carcinoma | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transitional cell carcinoma | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Peripheral artery aneurysm | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral artery stenosis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chest pain | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Asthenia | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pyrexia | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Multiple organ dysfunction syndrome | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Stent-graft endoleak | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Immune system disorders | | | | |
| Contrast media allergy | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Respiratory, thoracic and mediastinal disorders | | | | |
| Chronic obstructive pulmonary disease | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Atelectasis | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

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|---|---|---|---|---|
| Dyspnoea | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pleural effusion | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonitis | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pulmonary embolism | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Respiratory failure | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Psychiatric disorders | | | | |
| Anxiety | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Delirium | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Product issues | | | | |
| Device dislocation | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

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|---|---|---|---|
| Injury, poisoning and procedural complications | | | |
| Acetabulum fracture | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Joint dislocation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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|---|---|---|---|---|
| Cardiac failure | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiac arrest | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Atrial thrombosis | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Left ventricular failure | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Myocarditis | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pericardial effusion | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pericarditis | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Nervous system disorders | | | | |
| Aphasia | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bell's palsy | | | | |

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|---|---|---|---|---|
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cerebral infarction | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haemorrhage intracranial | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Encephalopathy | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haemorrhagic stroke | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Myasthenic syndrome | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lacunar infarction | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ischaemic stroke | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Neuropathy peripheral | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Neuritis | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Myelopathy | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Seizure | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Spinal cord compression | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Blood and lymphatic system disorders | | | | |
| Thrombocytopenia | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lymphadenopathy | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Febrile neutropenia | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal disorders | | | | |

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|---|---|---|---|---|
| Abdominal pain upper | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Constipation | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Colitis | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Diarrhoea | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ileus | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastric ulcer | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Oesophageal varices haemorrhage | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pancreatitis acute | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Rectal haemorrhage | | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Autoimmune hepatitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatotoxicity | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatitis cholestatic | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |

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|---|---|---|---|---|
| Nephritis | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Acute kidney injury | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Urinary retention | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Endocrine disorders | | | | |
| Adrenal insufficiency | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Secondary adrenocortical insufficiency | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Musculoskeletal and connective tissue disorders | | | | |
| Intervertebral disc protrusion | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Muscular weakness | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Myositis | | | | |

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|---|---|---|---|---|
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pathological fracture | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Polyarthritis | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infections and infestations | | | | |
| Abdominal abscess | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal bacterial infection | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Encephalitis | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cellulitis | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Escherichia sepsis | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bronchitis | | | | |

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|---|---|---|---|---|
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Influenza | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Urinary tract infection | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Sepsis | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Urosepsis | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Vascular device infection | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Metabolism and nutrition disorders | | | | |
| Hypercalcaemia | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Diabetic ketoacidosis | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Diabetes mellitus | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Adult failure to thrive | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Dehydration | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Type 2 diabetes mellitus | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Type 1 diabetes mellitus | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hypophosphataemia | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hyponatraemia | | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hyperglycaemia | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| **Non-serious adverse events** | Cohort B: nccRCC First Course | Cohort B: nccRCC Second Course | Cohort A: ccRCC First Course |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 142 / 165 (86.06%) | 3 / 5 (60.00%) | 105 / 110 (95.45%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 11 / 165 (6.67%) | 0 / 5 (0.00%) | 9 / 110 (8.18%) |
| occurrences (all) | 12 | 0 | 11 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 19 / 165 (11.52%) | 1 / 5 (20.00%) | 13 / 110 (11.82%) |
| occurrences (all) | 22 | 1 | 23 |
| Catheter site pain | | | |
| subjects affected / exposed | 2 / 165 (1.21%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Chest pain | | | |
| subjects affected / exposed | 9 / 165 (5.45%) | 0 / 5 (0.00%) | 7 / 110 (6.36%) |
| occurrences (all) | 10 | 0 | 7 |
| Fatigue | | | |
| subjects affected / exposed | 42 / 165 (25.45%) | 0 / 5 (0.00%) | 43 / 110 (39.09%) |
| occurrences (all) | 48 | 0 | 51 |
| Influenza like illness | | | |
| subjects affected / exposed | 7 / 165 (4.24%) | 0 / 5 (0.00%) | 10 / 110 (9.09%) |
| occurrences (all) | 13 | 0 | 24 |
| Oedema peripheral | | | |
| subjects affected / exposed | 14 / 165 (8.48%) | 0 / 5 (0.00%) | 8 / 110 (7.27%) |
| occurrences (all) | 16 | 0 | 9 |
| Pyrexia | | | |
| subjects affected / exposed | 17 / 165 (10.30%) | 1 / 5 (20.00%) | 8 / 110 (7.27%) |
| occurrences (all) | 21 | 1 | 8 |

| | | | |
|---|---|---|---|
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 165 (0.00%) | 0 / 5 (0.00%) | 0 / 110 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 26 / 165 (15.76%) | 0 / 5 (0.00%) | 25 / 110 (22.73%) |
| occurrences (all) | 30 | 0 | 30 |
| Dyspnoea | | | |
| subjects affected / exposed | 15 / 165 (9.09%) | 0 / 5 (0.00%) | 16 / 110 (14.55%) |
| occurrences (all) | 19 | 0 | 19 |
| Productive cough | | | |
| subjects affected / exposed | 9 / 165 (5.45%) | 0 / 5 (0.00%) | 2 / 110 (1.82%) |
| occurrences (all) | 11 | 0 | 2 |
| Wheezing | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 2 / 110 (1.82%) |
| occurrences (all) | 1 | 0 | 2 |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 6 / 165 (3.64%) | 0 / 5 (0.00%) | 8 / 110 (7.27%) |
| occurrences (all) | 7 | 0 | 8 |
| Insomnia | | | |
| subjects affected / exposed | 13 / 165 (7.88%) | 0 / 5 (0.00%) | 10 / 110 (9.09%) |
| occurrences (all) | 14 | 0 | 13 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 15 / 165 (9.09%) | 0 / 5 (0.00%) | 15 / 110 (13.64%) |
| occurrences (all) | 17 | 0 | 15 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 12 / 165 (7.27%) | 0 / 5 (0.00%) | 12 / 110 (10.91%) |
| occurrences (all) | 13 | 0 | 15 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 13 / 165 (7.88%) | 0 / 5 (0.00%) | 8 / 110 (7.27%) |
| occurrences (all) | 15 | 0 | 8 |
| Weight decreased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 10 / 165 (6.06%) | 0 / 5 (0.00%) | 4 / 110 (3.64%) |
| occurrences (all) | 10 | 0 | 4 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 3 / 165 (1.82%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences (all) | 9 | 0 | 1 |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 5 / 165 (3.03%) | 0 / 5 (0.00%) | 7 / 110 (6.36%) |
| occurrences (all) | 11 | 0 | 9 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 12 / 165 (7.27%) | 0 / 5 (0.00%) | 19 / 110 (17.27%) |
| occurrences (all) | 15 | 0 | 23 |
| Cardiac disorders | | | |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 1 / 5 (20.00%) | 1 / 110 (0.91%) |
| occurrences (all) | 1 | 1 | 2 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 18 / 165 (10.91%) | 0 / 5 (0.00%) | 13 / 110 (11.82%) |
| occurrences (all) | 24 | 0 | 17 |
| Dizziness | | | |
| subjects affected / exposed | 6 / 165 (3.64%) | 0 / 5 (0.00%) | 10 / 110 (9.09%) |
| occurrences (all) | 9 | 0 | 13 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 19 / 165 (11.52%) | 0 / 5 (0.00%) | 15 / 110 (13.64%) |
| occurrences (all) | 24 | 0 | 16 |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 18 / 165 (10.91%) | 0 / 5 (0.00%) | 23 / 110 (20.91%) |
| occurrences (all) | 23 | 0 | 23 |
| Abdominal pain | | | |
| subjects affected / exposed | 22 / 165 (13.33%) | 0 / 5 (0.00%) | 10 / 110 (9.09%) |
| occurrences (all) | 28 | 0 | 11 |
| Vomiting | | | |
| subjects affected / exposed | 27 / 165 (16.36%) | 0 / 5 (0.00%) | 8 / 110 (7.27%) |
| occurrences (all) | 37 | 0 | 9 |
| Nausea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 28 / 165 (16.97%) | 0 / 5 (0.00%) | 22 / 110 (20.00%) |
| occurrences (all) | 38 | 0 | 26 |
| Haemorrhoids | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 1 / 5 (20.00%) | 0 / 110 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Dyspepsia | | | |
| subjects affected / exposed | 6 / 165 (3.64%) | 0 / 5 (0.00%) | 8 / 110 (7.27%) |
| occurrences (all) | 6 | 0 | 8 |
| Dry mouth | | | |
| subjects affected / exposed | 15 / 165 (9.09%) | 0 / 5 (0.00%) | 13 / 110 (11.82%) |
| occurrences (all) | 18 | 0 | 16 |
| Diarrhoea | | | |
| subjects affected / exposed | 40 / 165 (24.24%) | 0 / 5 (0.00%) | 35 / 110 (31.82%) |
| occurrences (all) | 65 | 0 | 58 |
| Skin and subcutaneous tissue disorders | | | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 10 / 165 (6.06%) | 0 / 5 (0.00%) | 8 / 110 (7.27%) |
| occurrences (all) | 11 | 0 | 8 |
| Dry skin | | | |
| subjects affected / exposed | 10 / 165 (6.06%) | 0 / 5 (0.00%) | 7 / 110 (6.36%) |
| occurrences (all) | 11 | 0 | 9 |
| Pruritus | | | |
| subjects affected / exposed | 37 / 165 (22.42%) | 1 / 5 (20.00%) | 41 / 110 (37.27%) |
| occurrences (all) | 48 | 1 | 54 |
| Rash | | | |
| subjects affected / exposed | 19 / 165 (11.52%) | 0 / 5 (0.00%) | 17 / 110 (15.45%) |
| occurrences (all) | 24 | 0 | 23 |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 6 / 165 (3.64%) | 0 / 5 (0.00%) | 6 / 110 (5.45%) |
| occurrences (all) | 9 | 0 | 6 |
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 26 / 165 (15.76%) | 0 / 5 (0.00%) | 16 / 110 (14.55%) |
| occurrences (all) | 27 | 0 | 17 |
| Hyperthyroidism | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 11 / 165 (6.67%) | 0 / 5 (0.00%) | 6 / 110 (5.45%) |
| occurrences (all) | 11 | 0 | 6 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 29 / 165 (17.58%) | 0 / 5 (0.00%) | 37 / 110 (33.64%) |
| occurrences (all) | 40 | 0 | 54 |
| Back pain | | | |
| subjects affected / exposed | 22 / 165 (13.33%) | 0 / 5 (0.00%) | 12 / 110 (10.91%) |
| occurrences (all) | 28 | 0 | 13 |
| Groin pain | | | |
| subjects affected / exposed | 1 / 165 (0.61%) | 0 / 5 (0.00%) | 1 / 110 (0.91%) |
| occurrences (all) | 1 | 0 | 1 |
| Pain in extremity | | | |
| subjects affected / exposed | 15 / 165 (9.09%) | 0 / 5 (0.00%) | 7 / 110 (6.36%) |
| occurrences (all) | 15 | 0 | 7 |
| Myalgia | | | |
| subjects affected / exposed | 10 / 165 (6.06%) | 0 / 5 (0.00%) | 11 / 110 (10.00%) |
| occurrences (all) | 15 | 0 | 12 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 11 / 165 (6.67%) | 0 / 5 (0.00%) | 8 / 110 (7.27%) |
| occurrences (all) | 16 | 0 | 9 |
| Sinusitis | | | |
| subjects affected / exposed | 3 / 165 (1.82%) | 0 / 5 (0.00%) | 6 / 110 (5.45%) |
| occurrences (all) | 3 | 0 | 7 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 9 / 165 (5.45%) | 1 / 5 (20.00%) | 9 / 110 (8.18%) |
| occurrences (all) | 10 | 1 | 9 |
| Urinary tract infection | | | |
| subjects affected / exposed | 14 / 165 (8.48%) | 1 / 5 (20.00%) | 5 / 110 (4.55%) |
| occurrences (all) | 15 | 1 | 15 |
| Metabolism and nutrition disorders | | | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 7 / 165 (4.24%) | 0 / 5 (0.00%) | 8 / 110 (7.27%) |
| occurrences (all) | 10 | 0 | 18 |
| Hyperglycaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 165 (1.82%) | 0 / 5 (0.00%) | 7 / 110 (6.36%) |
| occurrences (all) | 3 | 0 | 9 |
| Hypercalcaemia | | | |
| subjects affected / exposed | 3 / 165 (1.82%) | 0 / 5 (0.00%) | 7 / 110 (6.36%) |
| occurrences (all) | 3 | 0 | 9 |
| Decreased appetite | | | |
| subjects affected / exposed | 25 / 165 (15.15%) | 0 / 5 (0.00%) | 22 / 110 (20.00%) |
| occurrences (all) | 29 | 0 | 24 |

| **Non-serious adverse events** | Cohort A: ccRCC Second Course | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 3 / 3 (100.00%) | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Catheter site pain | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | | |
| occurrences (all) | 1 | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pyrexia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | | |
| occurrences (all) | 1 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Productive cough | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Wheezing | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | | |
| occurrences (all) | 1 | | |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Insomnia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|---|---|---|---|
| Weight decreased<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0 | | |
| Neutrophil count decreased<br>subjects affected / exposed<br>occurrences (all) | 1 / 3 (33.33%)<br>1 | | |
| Lymphocyte count decreased<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0 | | |
| Blood creatinine increased<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0 | | |
| Cardiac disorders<br>Tachycardia<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0 | | |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0 | | |
| Dizziness<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0 | | |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0 | | |
| Gastrointestinal disorders<br>Constipation<br>subjects affected / exposed<br>occurrences (all) | 1 / 3 (33.33%)<br>1 | | |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0 | | |
| Vomiting<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0 | | |

| | | | |
|---|---|---|---|
| Nausea<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0 | | |
| Haemorrhoids<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0 | | |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0 | | |
| Dry mouth<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0 | | |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0 | | |
| Skin and subcutaneous tissue disorders<br>Rash maculo-papular<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0 | | |
| Dry skin<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0 | | |
| Pruritus<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0 | | |
| Rash<br>subjects affected / exposed<br>occurrences (all) | 1 / 3 (33.33%)<br>1 | | |
| Renal and urinary disorders<br>Haematuria<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0 | | |
| Endocrine disorders<br>Hypothyroidism<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0 | | |
| Hyperthyroidism | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | | |
| occurrences (all) | 1 | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Groin pain | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | | |
| occurrences (all) | 1 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Myalgia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | | |
| occurrences (all) | 1 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Metabolism and nutrition disorders | | | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hyperglycaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 18 April 2017 | Amendment 1 clarified eligibility so that inclusion and exclusion criteria were not overly restrictive, and provided a clear and concise guide to investigators on management of AEs associated with pembrolizumab. Additionally, the amendment allowed enrollment in Cohort B upon local laboratory confirmation of diagnosis, and central laboratory confirmation that the submitted tissue is adequate for central review (previously, central laboratory diagnosis confirmation was required before allocation). |
| 20 November 2017 | Amendment 2 updated the dose modification and toxicity management guidelines for pembrolizumab in order to be in alignment with the most current label and safety information for pembrolizumab. The amendment also changed the timing of bone scans at screening (accepting scans that have been performed within 42 days of screening). |
| 02 December 2020 | Amendment 3 removed reference to "sub-trial" in the Future Biomarker Research (FBR) sections of the protocol. |
| 09 July 2021 | Amendment 4 updated the dose modification and toxicity management guidelines for immune-related adverse events (irAEs). |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported