



Clinical trial results:

Phase II Trial of Pembrolizumab (MK-3475) in Subjects with Metastatic Castration-Resistant Prostate Cancer (mCRPC) (KEYNOTE-199)

Summary

| | |
|--------------------------|----------------------------------|
| EudraCT number | 2015-003644-40 |
| Trial protocol | FI IE DE SE ES EE NL PL FR GB IT |
| Global end of trial date | 28 February 2022 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 11 March 2023 |
| First version publication date | 11 March 2023 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | 3475-199 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|--|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02787005 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Merck: KEYNOTE-199, Merck: MK-3475-199 |

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 | 28 February 2022 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 28 February 2022 |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 February 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

This was a study of pembrolizumab (MK-3475) in participants with metastatic castration-resistant prostate cancer (mCRPC). Participants were enrolled into one of five cohorts: Cohort 1 (participants with programmed cell death ligand 1 [PD-L1]-positive, measurable disease), Cohort 2 (participants with PD-L1 negative, measurable disease), Cohort 3 (participants with bone-metastases and non-measurable disease) post-chemotherapy, Cohort 4 (participants with Response Evaluation Criteria in Solid Tumors version 1.1- [RECIST 1.1]-measurable disease) and Cohort 5 (participants with bone metastases only or bone-predominant disease) pre-chemotherapy.

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:

Participants in Cohorts 4 and 5 received pembrolizumab monotherapy with their current, stable standard of care (SOC) regimen of enzalutamide. The dose of enzalutamide was the same dose each participant was receiving before the start of pembrolizumab treatment. Note: participants in Cohorts 4 and 5 may have received abiraterone prior to enzalutamide.

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 01 July 2016 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Australia: 17 |
| Country: Number of subjects enrolled | Canada: 16 |
| Country: Number of subjects enrolled | Estonia: 7 |
| Country: Number of subjects enrolled | Finland: 14 |
| Country: Number of subjects enrolled | France: 21 |
| Country: Number of subjects enrolled | Germany: 7 |
| Country: Number of subjects enrolled | Hong Kong: 2 |
| Country: Number of subjects enrolled | Ireland: 8 |
| Country: Number of subjects enrolled | Israel: 27 |
| Country: Number of subjects enrolled | Italy: 7 |
| Country: Number of subjects enrolled | Japan: 23 |
| Country: Number of subjects enrolled | Korea, Republic of: 5 |
| Country: Number of subjects enrolled | Netherlands: 28 |

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Poland: 7 |
| Country: Number of subjects enrolled | Spain: 27 |
| Country: Number of subjects enrolled | Sweden: 14 |
| Country: Number of subjects enrolled | Switzerland: 21 |
| Country: Number of subjects enrolled | Taiwan: 1 |
| Country: Number of subjects enrolled | Turkey: 8 |
| Country: Number of subjects enrolled | United Kingdom: 23 |
| Country: Number of subjects enrolled | United States: 105 |
| Worldwide total number of subjects | 388 |
| EEA total number of subjects | 140 |

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) | 105 |
| From 65 to 84 years | 272 |
| 85 years and over | 11 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Male subjects at least 18 years of age with Metastatic Castration-resistant Prostate Cancer (mCRPC) were screened for enrollment in the study. Per protocol, response/progression or adverse events (AEs) that occurred during the second course were not counted towards efficacy outcome measures or safety outcome measures, respectively.

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 1: PD-L1 positive with measurable disease |
|------------------|--|

Arm description:

Participants with PD-L1-positive, measurable disease received pembrolizumab 200 mg via intravenous (IV) infusion on Day 1 of every 3-week cycle for up to 2 years. Eligible participants who stopped the initial course of pembrolizumab with Stable Disease (SD) or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab for up to 17 cycles (up to approximately 1 additional year) at the investigator's discretion.

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Pembrolizumab |
| Investigational medicinal product code | |
| Other name | MK-3475 KEYTRUDA® |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

200 mg via IV every 3-week cycle

| | |
|------------------|--|
| Arm title | Cohort 2: PD-L1 negative with measurable disease |
|------------------|--|

Arm description:

Participants with PD-L1 negative, measurable disease received pembrolizumab 200 mg via IV infusion on Day 1 of every 3-week cycle for up to 2 years. Eligible participants who stopped the initial course of pembrolizumab with SD or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab for up to 17 cycles (up to approximately 1 additional year) at the investigator's discretion.

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Pembrolizumab |
| Investigational medicinal product code | |
| Other name | MK-3475 KEYTRUDA® |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

200 mg via IV every 3-week cycle

| | |
|------------------|---|
| Arm title | Cohort 3: Bone metastases with non-measurable disease |
|------------------|---|

Arm description:

Participants with bone metastases and non-measurable disease received pembrolizumab 200 mg via IV

infusion on Day 1 of every 3-week cycle for up to 2 years. Eligible participants who stopped the initial course of pembrolizumab with SD or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab for up to 17 cycles (up to approximately 1 additional year) at the investigator's discretion.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Pembrolizumab |
| Investigational medicinal product code | |
| Other name | MK-3475 KEYTRUDA® |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: 200 mg via IV every 3-week cycle | |
| Arm title | Cohort 4: RECIST 1.1-measurable disease |

Arm description:

Participants with RECIST 1.1-measurable disease received pembrolizumab 200 mg via IV infusion on Day 1 of every 3-week cycle. Eligible participants who stopped the initial course of pembrolizumab with SD or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab for up to 17 cycles (up to approximately 1 additional year) at the investigator's discretion.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Pembrolizumab |
| Investigational medicinal product code | |
| Other name | MK-3475 KEYTRUDA® |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: 200 mg via IV every 3-week cycle | |
| Arm title | Cohort 5: Bone metastases only or bone-predominant disease |

Arm description:

Participants with bone metastases only or bone-predominant disease received pembrolizumab 200 mg via IV infusion on Day 1 of every 3-week cycle. Eligible participants who stopped the initial course of pembrolizumab with SD or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab for up to 17 cycles (up to approximately 1 additional year) at the investigator's discretion.

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Pembrolizumab |
| Investigational medicinal product code | |
| Other name | MK-3475 KEYTRUDA® |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: 200 mg via IV every 3-week cycle | |

| Number of subjects in period 1 | Cohort 1: PD-L1 positive with measurable disease | Cohort 2: PD-L1 negative with measurable disease | Cohort 3: Bone metastases with non-measurable disease |
|--------------------------------|--|--|---|
| | | | |
| Started | 133 | 69 | 58 |
| Treated | 133 | 67 | 58 |
| Received 2nd course | 1 | 0 | 0 |
| Completed | 0 | 0 | 0 |
| Not completed | 133 | 69 | 58 |
| Consent withdrawn by subject | 2 | 1 | 1 |
| Screen Failure | - | 2 | - |
| Adverse event, non-fatal | 24 | 9 | 9 |
| Death | 100 | 53 | 48 |
| Sponsor Decision | 7 | 4 | - |
| Lost to follow-up | - | - | - |

| Number of subjects in period 1 | Cohort 4: RECIST 1.1-measurable disease | Cohort 5: Bone metastases only or bone-predominant disease |
|--------------------------------|---|--|
| | | |
| Started | 81 | 47 |
| Treated | 81 | 45 |
| Received 2nd course | 0 | 0 |
| Completed | 0 | 0 |
| Not completed | 81 | 47 |
| Consent withdrawn by subject | - | 1 |
| Screen Failure | - | 1 |
| Adverse event, non-fatal | 7 | 2 |
| Death | 69 | 38 |
| Sponsor Decision | 4 | 5 |
| Lost to follow-up | 1 | - |

Baseline characteristics

Reporting groups

| | |
|--|--|
| Reporting group title | Cohort 1: PD-L1 positive with measurable disease |
| Reporting group description: Participants with PD-L1-positive, measurable disease received pembrolizumab 200 mg via intravenous (IV) infusion on Day 1 of every 3-week cycle for up to 2 years. Eligible participants who stopped the initial course of pembrolizumab with Stable Disease (SD) or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab for up to 17 cycles (up to approximately 1 additional year) at the investigator's discretion. | |
| Reporting group title | Cohort 2: PD-L1 negative with measurable disease |
| Reporting group description: Participants with PD-L1 negative, measurable disease received pembrolizumab 200 mg via IV infusion on Day 1 of every 3-week cycle for up to 2 years. Eligible participants who stopped the initial course of pembrolizumab with SD or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab for up to 17 cycles (up to approximately 1 additional year) at the investigator's discretion. | |
| Reporting group title | Cohort 3: Bone metastases with non-measurable disease |
| Reporting group description: Participants with bone metastases and non-measurable disease received pembrolizumab 200 mg via IV infusion on Day 1 of every 3-week cycle for up to 2 years. Eligible participants who stopped the initial course of pembrolizumab with SD or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab for up to 17 cycles (up to approximately 1 additional year) at the investigator's discretion. | |
| Reporting group title | Cohort 4: RECIST 1.1-measurable disease |
| Reporting group description: Participants with RECIST 1.1-measurable disease received pembrolizumab 200 mg via IV infusion on Day 1 of every 3-week cycle. Eligible participants who stopped the initial course of pembrolizumab with SD or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab for up to 17 cycles (up to approximately 1 additional year) at the investigator's discretion. | |
| Reporting group title | Cohort 5: Bone metastases only or bone-predominant disease |
| Reporting group description: Participants with bone metastases only or bone-predominant disease received pembrolizumab 200 mg via IV infusion on Day 1 of every 3-week cycle. Eligible participants who stopped the initial course of pembrolizumab with SD or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab for up to 17 cycles (up to approximately 1 additional year) at the investigator's discretion. | |

| Reporting group values | Cohort 1: PD-L1 positive with measurable disease | Cohort 2: PD-L1 negative with measurable disease | Cohort 3: Bone metastases with non-measurable disease |
|--|--|--|---|
| Number of subjects | 133 | 69 | 58 |
| Age Categorical Units: Subjects | | | |
| In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years | | | |

| | | | |
|-------------------|--|--|--|
| 85 years and over | | | |
|-------------------|--|--|--|

| | | | |
|---|---------------|---------------|---------------|
| Age Continuous Units: years arithmetic mean standard deviation | 67.9 ± 7.6 | 68.6 ± 7.2 | 69.4 ± 7.1 |
| Gender Categorical Units: Participants | | | |
| Female | 0 | 0 | 0 |
| Male | 133 | 69 | 58 |
| Race Units: Subjects | | | |
| Asian | 13 | 6 | 7 |
| Black of African American | 3 | 1 | 1 |
| Multiple | 0 | 0 | 0 |
| White | 109 | 52 | 48 |
| Missing | 8 | 10 | 2 |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 3 | 4 | 1 |
| Not Hispanic or Latino | 121 | 55 | 55 |
| Not Reported | 6 | 5 | 2 |
| Unknown | 3 | 5 | 0 |

| Reporting group values | Cohort 4: RECIST 1.1-measurable disease | Cohort 5: Bone metastases only or bone-predominant disease | Total |
|---|---|--|-------|
| Number of subjects | 81 | 47 | 388 |
| Age Categorical Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Newborns (0-27 days) | | | |
| Infants and toddlers (28 days-23 months) | | | |
| Children (2-11 years) | | | |
| Adolescents (12-17 years) | | | |
| Adults (18-64 years) | | | |
| From 65-84 years | | | |
| 85 years and over | | | |
| Age Continuous Units: years arithmetic mean standard deviation | 73.1 ± 8.4 | 69.7 ± 9.5 | - |
| Gender Categorical Units: Participants | | | |
| Female | 0 | 0 | 0 |
| Male | 81 | 47 | 388 |

| | | | |
|---------------------------|----|----|-----|
| Race | | | |
| Units: Subjects | | | |
| Asian | 5 | 2 | 33 |
| Black or African American | 3 | 3 | 11 |
| Multiple | 1 | 0 | 1 |
| White | 70 | 42 | 321 |
| Missing | 2 | 0 | 22 |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 3 | 3 | 14 |
| Not Hispanic or Latino | 76 | 44 | 351 |
| Not Reported | 2 | 0 | 15 |
| Unknown | 0 | 0 | 8 |

End points

End points reporting groups

| | |
|--|--|
| Reporting group title | Cohort 1: PD-L1 positive with measurable disease |
| Reporting group description: Participants with PD-L1-positive, measurable disease received pembrolizumab 200 mg via intravenous (IV) infusion on Day 1 of every 3-week cycle for up to 2 years. Eligible participants who stopped the initial course of pembrolizumab with Stable Disease (SD) or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab for up to 17 cycles (up to approximately 1 additional year) at the investigator's discretion. | |
| Reporting group title | Cohort 2: PD-L1 negative with measurable disease |
| Reporting group description: Participants with PD-L1 negative, measurable disease received pembrolizumab 200 mg via IV infusion on Day 1 of every 3-week cycle for up to 2 years. Eligible participants who stopped the initial course of pembrolizumab with SD or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab for up to 17 cycles (up to approximately 1 additional year) at the investigator's discretion. | |
| Reporting group title | Cohort 3: Bone metastases with non-measurable disease |
| Reporting group description: Participants with bone metastases and non-measurable disease received pembrolizumab 200 mg via IV infusion on Day 1 of every 3-week cycle for up to 2 years. Eligible participants who stopped the initial course of pembrolizumab with SD or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab for up to 17 cycles (up to approximately 1 additional year) at the investigator's discretion. | |
| Reporting group title | Cohort 4: RECIST 1.1-measurable disease |
| Reporting group description: Participants with RECIST 1.1-measurable disease received pembrolizumab 200 mg via IV infusion on Day 1 of every 3-week cycle. Eligible participants who stopped the initial course of pembrolizumab with SD or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab for up to 17 cycles (up to approximately 1 additional year) at the investigator's discretion. | |
| Reporting group title | Cohort 5: Bone metastases only or bone-predominant disease |
| Reporting group description: Participants with bone metastases only or bone-predominant disease received pembrolizumab 200 mg via IV infusion on Day 1 of every 3-week cycle. Eligible participants who stopped the initial course of pembrolizumab with SD or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab for up to 17 cycles (up to approximately 1 additional year) at the investigator's discretion. | |
| Subject analysis set title | Cohort 1 |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Participants with PD-L1-positive, measurable disease received pembrolizumab 200 mg via IV infusion on Day 1 of every 3-week cycle for up to 2 years. | |
| Subject analysis set title | Cohort 2 |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Participants with PD-L1 negative, measurable disease received pembrolizumab 200 mg via IV infusion on Day 1 of every 3-week cycle for up to 2 years. | |
| Subject analysis set title | Cohort 3 |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Participants with bone metastases and non-measurable disease received pembrolizumab 200 mg via IV infusion on Day 1 of every 3-week cycle for up to 2 years. | |
| Subject analysis set title | Cohort 4 |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Participants with RECIST 1.1-measurable disease received pembrolizumab 200 mg via IV infusion on | |

Day 1 of every 3-week cycle.

| | |
|----------------------------|--------------------|
| Subject analysis set title | Cohort 5 |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Participants with bone metastases only or bone-predominant disease received pembrolizumab 200 mg via IV infusion on Day 1 of every 3-week cycle.

| | |
|----------------------------|--------------------------|
| Subject analysis set title | Cohorts 1 and 2 Combined |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Participants with PD-L1-positive, measurable disease or PD-L1 negative, measurable disease received pembrolizumab 200 mg via IV infusion on Day 1 of every 3-week cycle for up to 2 years.

| | |
|----------------------------|------------------------------|
| Subject analysis set title | Cohorts 1, 2, and 3 Combined |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Participants with PD-L1-positive, measurable disease, PD-L1 negative, measurable disease or bone metastases and non-measurable disease received pembrolizumab 200 mg via IV infusion on Day 1 of every 3-week cycle for up to 2 years.

| | |
|----------------------------|--------------------------|
| Subject analysis set title | Cohorts 4 and 5 Combined |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Participants with RECIST 1.1-measurable disease or bone metastases only or bone-predominant disease received pembrolizumab 200 mg via IV infusion on Day 1 of every 3-week cycle.

Primary: Objective Response Rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (Cohort 1, Cohort 2, Cohort 4 and Cohorts 1 and 2 Combined)

| | |
|-----------------|---|
| End point title | Objective Response Rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (Cohort 1, Cohort 2, Cohort 4 and Cohorts 1 and 2 Combined) ^[1] |
|-----------------|---|

End point description:

ORR was defined as the percentage of participants who experienced 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) and was assessed using RECIST 1.1 by central imaging vendor. Per protocol, analysis for this outcome measure was conducted in Cohorts 1 and 2 combined, as well as in Cohorts 1, 2, and 4 separately for the first course of treatment. Analysis population was the All Subjects as Treated (ASaT) which consisted of all allocated participants who received at least 1 dose of study treatment.

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

End point timeframe:

Up to ~52 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 analysis was planned for this endpoint.

| End point values | Cohort 1 | Cohort 2 | Cohort 4 | Cohorts 1 and 2 Combined |
|-----------------------------------|----------------------|----------------------|----------------------|--------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 133 | 67 | 81 | 200 |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 6.0 (2.6 to 11.5) | 3.0 (0.4 to 10.4) | 12.3 (6.1 to 21.5) | 5.0 (2.4 to 9.0) |

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

An AE was defined as any unfavorable and unintended sign, symptom, disease, or worsening of preexisting condition temporally associated with study treatment and irrespective of causality to study treatment. The percentage of participants that experienced at least one AE for the first course of treatment was reported. Analysis population was the ASaT which consisted of all allocated participants who received at least 1 dose of study treatment for the first course of treatment.

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

End point timeframe:

Up to 52 months

| End point values | Cohort 1: PD-L1 positive with measurable disease | Cohort 2: PD-L1 negative with measurable disease | Cohort 3: Bone metastases with non-measurable disease | Cohort 4: RECIST 1.1-measurable disease |
|-----------------------------------|--|--|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 133 | 67 | 58 | 81 |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 99.2 | 97.0 | 100.0 | 98.8 |

| End point values | Cohort 5: Bone metastases only or bone-predominant disease | | | |
|-----------------------------------|--|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 45 | | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 97.8 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Discontinued Study Treatment Due to an AE

| | |
|-----------------|--|
| End point title | Percentage of Participants Who Discontinued Study Treatment Due to an AE |
|-----------------|--|

End point description:

An AE was defined as any unfavorable and unintended sign, symptom, disease, or worsening of preexisting condition temporally associated with study treatment and irrespective of causality to study treatment. The percentage of participants who discontinued study treatment during the first course of treatment due to an AE was reported. Analysis population was the ASaT which consisted of all allocated

participants who received at least 1 dose of study treatment for the first course of treatment.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to 52 months | |

| End point values | Cohort 1: PD-L1 positive with measurable disease | Cohort 2: PD-L1 negative with measurable disease | Cohort 3: Bone metastases with non-measurable disease | Cohort 4: RECIST 1.1-measurable disease |
|-----------------------------------|--|--|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 133 | 67 | 58 | 81 |
| Units: Percentage pf Participants | | | | |
| number (not applicable) | 10.5 | 3.0 | 12.1 | 18.5 |

| End point values | Cohort 5: Bone metastases only or bone-predominant disease | | | |
|-----------------------------------|--|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 45 | | | |
| Units: Percentage pf Participants | | | | |
| number (not applicable) | 20.0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) (By Each Cohort, Cohorts 1 and 2 Combined, Cohorts 1, 2, and 3 Combined, Cohorts 4 and 5 Combined)

| | |
|-----------------|---|
| End point title | Disease Control Rate (DCR) (By Each Cohort, Cohorts 1 and 2 Combined, Cohorts 1, 2, and 3 Combined, Cohorts 4 and 5 Combined) |
|-----------------|---|

End point description:

Percentage of participants who had CR (disappearance of all target lesions) or PR (at least a 30% decrease in the sum of diameters of target lesions) or stable disease (SD; Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease) for at least 6 months, by central imaging vendor where progressive disease (PD) in bone-only tumors were determined by radionuclide bone scan using Prostate Cancer Working Group (PCWG3) criteria and PD for all other tumors was determined using RECIST 1.1. Per protocol, analysis for this outcome measure was conducted in Cohorts 1 and 2 combined, Cohorts 1,2, and 3 combined, Cohorts 4 and 5 combined well as in Cohorts 1 to 5 separately for the first course of treatment. Analysis population was the ASaT which consisted of all allocated participants who received at least 1 dose of study treatment.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to ~52 months | |

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | Cohort 4 |
|-----------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 133 | 67 | 58 | 81 |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 10.5 (5.9 to 17.0) | 4.5 (0.9 to 12.5) | 24.1 (13.9 to 37.2) | 29.6 (20.0 to 40.8) |

| End point values | Cohort 5 | Cohorts 1 and 2 Combined | Cohorts 1, 2, and 3 Combined | Cohorts 4 and 5 Combined |
|-----------------------------------|----------------------|--------------------------|------------------------------|--------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 45 | 200 | 258 | 126 |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 31.1 (18.2 to 46.6) | 8.5 (5.0 to 13.3) | 12.0 (8.3 to 16.6) | 30.2 (22.3 to 39.0) |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) per PCWG3-modified RECIST 1.1 (Cohort 1, Cohort 2, Cohort 4 and Cohorts 1 and 2 Combined)

| | |
|-----------------|--|
| End point title | Duration of Response (DOR) per PCWG3-modified RECIST 1.1 (Cohort 1, Cohort 2, Cohort 4 and Cohorts 1 and 2 Combined) |
|-----------------|--|

End point description:

DOR was defined as the time from first documented evidence of complete response (CR; disappearance of all target lesions) or partial response (PR; $\geq 30\%$ decrease in the sum of diameters of target lesions) until progressive disease (PD) assessed by central imaging where PD was determined by radionuclide bone scan using Prostate Cancer Working Group (PCWG3)-modified RECIST 1.1 criteria and PD for all other tumors was determined using RECIST 1.1 or death due to any cause, whichever occurred first. 9999 indicated that the median and/or lower/upper limit was not reached due to an insufficient number of responding participants with relapse. Per protocol, analysis for this outcome measure was conducted in Cohorts 1, 2 and 4 separately, and in Cohorts 1 and 2 combined for the 1st course of treatment. The analysis was based on all responders with measurable disease at baseline in the ASaT population which consisted of all allocated participants who received at least 1 dose of study treatment.

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

End point timeframe:

Up to ~52 months

| End point values | Cohort 1 | Cohort 2 | Cohort 4 | Cohorts 1 and 2 Combined |
|-------------------------------|----------------------|----------------------|----------------------|--------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 8 | 2 | 10 | 10 |
| Units: Months | | | | |
| median (full range (min-max)) | 9999 (1.9 to 9999) | 9999 (4.4 to 9999) | 9999 (9999 to 9999) | 9999 (1.9 to 9999) |

Statistical analyses

No statistical analyses for this end point

Secondary: DOR- per RECIST 1.1 (Cohort 1, Cohort 2, Cohort 4 and Cohorts 1 and 2 Combined)

| | |
|-----------------|---|
| End point title | DOR- per RECIST 1.1 (Cohort 1, Cohort 2, Cohort 4 and Cohorts 1 and 2 Combined) |
|-----------------|---|

End point description:

DOR was defined as the time from first documented evidence of complete response (CR; disappearance of all target lesions) or partial response (PR; $\geq 30\%$ decrease in the sum of diameters of target lesions) until progressive disease (PD) assessed by central imaging where PD was determined by radionuclide bone scan using RECIST 1.1 and PD for all other tumors was determined using RECIST 1.1 or death due to any cause, whichever occurred first. 9999 indicated that the median and/or upper or lower limit was not reached due to an insufficient number of responding participants with relapse. Per protocol, analysis for this outcome measure was conducted in Cohorts 1, 2 and 4 separately, well as in Cohorts 1 and 2 combined for the first course of treatment. The analysis was based on all responders with measurable disease at baseline in the ASaT population which consisted of all allocated participants who received at least 1 dose of study treatment.

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

End point timeframe:

Up to ~52 months

| End point values | Cohort 1 | Cohort 2 | Cohort 4 | Cohorts 1 and 2 Combined |
|-------------------------------|----------------------|----------------------|----------------------|--------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 8 | 2 | 10 | 10 |
| Units: Months | | | | |
| median (full range (min-max)) | 9999 (1.9 to 9999) | 9999 (4.4 to 9999) | 9999 (9999 to 9999) | 9999 (1.9 to 9999) |

Statistical analyses

No statistical analyses for this end point

Secondary: Prostate-specific Antigen (PSA) Response Rate (By Each Cohort, Cohorts 1 and 2 Combined, Cohorts 1, 2, and 3 Combined, Cohorts 4 and 5 Combined)

| | |
|-----------------|--|
| End point title | Prostate-specific Antigen (PSA) Response Rate (By Each Cohort, Cohorts 1 and 2 Combined, Cohorts 1, 2, and 3 Combined, Cohorts 4 and 5 Combined) |
|-----------------|--|

End point description:

Percentage of participants who had PSA response defined as at least 50% decline from baseline measured twice at least 3 weeks apart. Per protocol, analysis for this outcome measure was conducted in Cohorts 1 and 2 combined, Cohorts 1, 2, and 3 combined, Cohorts 4 and 5 combined well as in Cohorts 1 to 5 separately for the first course of treatment. Analysis population was the ASaT which consisted of all allocated participants who received at least one dose of study treatment and had a PSA measurement at baseline.

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

End point timeframe:

Up to ~52 months

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | Cohort 4 |
|-----------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 124 | 61 | 58 | 80 |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 6.5 (2.8 to 12.3) | 8.2 (2.7 to 18.1) | 1.7 (0.0 to 9.2) | 16.3 (8.9 to 26.2) |

| End point values | Cohort 5 | Cohorts 1 and 2 Combined | Cohorts 1, 2, and 3 Combined | Cohorts 4 and 5 Combined |
|-----------------------------------|----------------------|--------------------------|------------------------------|--------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 45 | 185 | 243 | 125 |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 8.9 (2.5 to 21.2) | 7.0 (3.8 to 11.7) | 5.8 (3.2 to 9.5) | 13.6 (8.1 to 20.9) |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to PSA Progression (By Each Cohort, Cohorts 1 and 2 Combined, Cohorts 1, 2, and 3 Combined, Cohorts 4 and 5 Combined)

| | |
|-----------------|--|
| End point title | Time to PSA Progression (By Each Cohort, Cohorts 1 and 2 Combined, Cohorts 1, 2, and 3 Combined, Cohorts 4 and 5 Combined) |
|-----------------|--|

End point description:

Time to PSA progression was defined as the time from first day of study treatment to the date of PSA progression. Participants without PSA progression were censored at the last PSA assessment date. PSA progression was defined as the date that an increase of 25% or more and an absolute increase of 2 ng/mL or more from the nadir were documented. For participants who had a decline in PSA during treatment, PSA progression must have been confirmed by a second value 3 or more weeks later increased with respect to the nadir PSA. 9999 indicated that the upper limit of the 95% CI was not reached due to insufficient number of participants with an event. Per protocol, analysis for this outcome measure was conducted in Cohorts 1 and 2 combined, Cohorts 1,2, and 3 combined, Cohorts 4 and 5 combined well as in Cohorts 1 to 5 separately for the first course of treatment. Analysis population was the ASaT which consisted of all allocated participants who received at least 1 dose of study treatment.

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

End point timeframe:

Up to ~52 months

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | Cohort 4 |
|----------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 133 | 67 | 58 | 81 |
| Units: Months | | | | |
| median (confidence interval 95%) | 5.1 (4.2 to 9999) | 6.2 (4.2 to 6.9) | 4.2 (4.2 to 4.6) | 5.6 (4.2 to 10.4) |

| End point values | Cohort 5 | Cohorts 1 and 2 Combined | Cohorts 1, 2, and 3 Combined | Cohorts 4 and 5 Combined |
|----------------------------------|----------------------|--------------------------|------------------------------|--------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 45 | 200 | 258 | 126 |
| Units: Months | | | | |
| median (confidence interval 95%) | 4.2 (4.2 to 6.2) | 6.2 (4.2 to 6.9) | 4.4 (4.2 to 6.2) | 4.4 (4.2 to 6.2) |

Statistical analyses

No statistical analyses for this end point

Secondary: Radiographic progression-free survival (rPFS) – per PCWG3-modified RECIST 1.1 (By Each Cohort, Cohorts 1 and 2 Combined, Cohorts 1, 2, and 3 Combined, Cohorts 4 and 5 Combined)

| | |
|-----------------|--|
| End point title | Radiographic progression-free survival (rPFS) – per PCWG3-modified RECIST 1.1 (By Each Cohort, Cohorts 1 and 2 Combined, Cohorts 1, 2, and 3 Combined, Cohorts 4 and 5 Combined) |
|-----------------|--|

End point description:

rPFS was defined as the time from first day of study treatment to the documented disease progression by central imaging vendor where PD in bone-only tumors was determined by radionuclide bone scan using PCWG3 criteria and PD for all other tumors were determined using RECIST 1.1 or death due to any cause, whichever occurs first. Per protocol, analysis for this outcome measure was conducted in Cohorts 1 and 2 combined, Cohorts 1,2, and 3 combined, Cohorts 4 and 5 combined well as in Cohorts 1 to 5 separately for the first course of treatment. Analysis population was the ASaT which consisted of all allocated participants who received at least 1 dose of study treatment.

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

End point timeframe:

Up to ~52 months

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | Cohort 4 |
|----------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 133 | 67 | 58 | 81 |
| Units: Months | | | | |
| median (confidence interval 95%) | 2.1 (2.0 to 2.1) | 2.1 (2.0 to 3.2) | 3.7 (2.1 to 4.2) | 4.2 (2.5 to 6.0) |

| End point values | Cohort 5 | Cohorts 1 and 2 Combined | Cohorts 1, 2, and 3 Combined | Cohorts 4 and 5 Combined |
|----------------------------------|----------------------|--------------------------|------------------------------|--------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 45 | 200 | 258 | 126 |
| Units: Months | | | | |
| median (confidence interval 95%) | 4.4 (3.2 to 6.2) | 2.1 (2.0 to 2.1) | 2.1 (2.1 to 2.2) | 4.2 (3.7 to 6.0) |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) (By Each Cohort, Cohorts 1 and 2 Combined, Cohorts 1, 2, and 3 Combined, Cohorts 4 and 5 Combined)

| | |
|-----------------|--|
| End point title | Overall Survival (OS) (By Each Cohort, Cohorts 1 and 2 Combined, Cohorts 1, 2, and 3 Combined, Cohorts 4 and 5 Combined) |
|-----------------|--|

End point description:

OS was defined as the time from first day of study treatment to the time of death. Participants without documented death were censored at the date of the last follow up. The OS was calculated using the product-limit (Kaplan-Meier) method for censored data. Per protocol, analysis for this outcome measure was conducted in Cohorts 1 and 2 combined, Cohorts 1,2, and 3 combined, Cohorts 4 and 5 combined well as in Cohorts 1 to 5 separately. Analysis population was the ASaT which consisted of all allocated participants who received at least 1 dose of study treatment for the first course of treatment.

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

End point timeframe:

Up to ~52 months

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | Cohort 4 |
|----------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 133 | 67 | 58 | 81 |
| Units: Months | | | | |
| median (confidence interval 95%) | 9.5 (6.4 to 11.9) | 7.9 (5.9 to 10.2) | 14.1 (10.8 to 17.6) | 17.6 (14.0 to 22.6) |

| End point values | Cohort 5 | Cohorts 1 and 2 Combined | Cohorts 1, 2, and 3 Combined | Cohorts 4 and 5 Combined |
|------------------|----------|--------------------------|------------------------------|--------------------------|
|------------------|----------|--------------------------|------------------------------|--------------------------|

| | | | | |
|----------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 45 | 200 | 258 | 126 |
| Units: Months | | | | |
| median (confidence interval 95%) | 20.8 (14.1 to 28.9) | 8.1 (6.6 to 10.7) | 9.6 (7.9 to 12.4) | 18.9 (16.2 to 23.6) |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of PSA response (Cohorts 4 and 5 by Cohort and Combined)

| | |
|---|---|
| End point title | Duration of PSA response (Cohorts 4 and 5 by Cohort and Combined) |
| End point description: | |
| Duration of PSA response was defined as the time from PSA response, when the PSA value first declined by at least 50% of the baseline (must have been confirmed by a second value), to the date of PSA progression at which there was an increase of 25% or more from the nadir PSA, provided the absolute increase from the nadir PSA was at least 2 ng/mL. 9999 indicates upper limit was not reached due to no progressive disease by the time of last disease assessment. Per protocol, analysis for this outcome measure was conducted in Cohorts 4 and 5 separately as well as combined for the first course of treatment. Analysis population was the ASaT which consisted of all allocated participants who received at least 1 dose of study treatment and had a confirmed PSA response. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to ~52 months | |

| End point values | Cohort 4 | Cohort 5 | Cohorts 4 and 5 Combined | |
|-------------------------------|----------------------|----------------------|--------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 13 | 4 | 17 | |
| Units: Months | | | | |
| median (full range (min-max)) | 8.3 (2.8 to 9999) | 18.0 (3.0 to 9999) | 18.0 (2.8 to 9999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Initiation of Cytotoxic Chemotherapy (Cohorts 4 and 5 by Cohort and Combined)

| | |
|--|---|
| End point title | Time to Initiation of Cytotoxic Chemotherapy (Cohorts 4 and 5 by Cohort and Combined) |
| End point description: | |
| Time to initiation of cytotoxic chemotherapy was defined as the time from first day of study treatment to the time of initiation of cytotoxic chemotherapy for prostate cancer. The median time was calculated using the Kaplan-Meier method for censored data. Per protocol, analysis for this outcome measure was conducted in Cohorts 4 and 5 separately as well as combined for the first course of treatment. Analysis population was the ASaT which consisted of all allocated participants who received at least 1 dose of study treatment. | |

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to ~52 months | |

| End point values | Cohort 4 | Cohort 5 | Cohorts 4 and 5 Combined | |
|----------------------------------|----------------------|----------------------|--------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 81 | 45 | 126 | |
| Units: Months | | | | |
| median (confidence interval 95%) | 11.1 (8.5 to 17.4) | 11.3 (9.0 to 14.5) | 11.1 (9.4 to 14.5) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to New-Anticancer Therapy (Cohorts 4 and 5 by Cohort and Combined)

| | |
|-----------------|---|
| End point title | Time to New-Anticancer Therapy (Cohorts 4 and 5 by Cohort and Combined) |
|-----------------|---|

End point description:

Time to new-anticancer therapy was defined as the time from first day of study treatment to the time of new-anticancer therapy for prostate cancer. The median time was calculated using the Kaplan-Meier method for censored data. Per protocol, analysis for this outcome measure was conducted in Cohorts 4 and 5 separately as well as combined for the first course of treatment. Analysis population was the ASaT which consisted of all allocated participants who received at least 1 dose of study treatment.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to ~52 months | |

| End point values | Cohort 4 | Cohort 5 | Cohorts 4 and 5 Combined | |
|----------------------------------|----------------------|----------------------|--------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 81 | 45 | 126 | |
| Units: Months | | | | |
| median (confidence interval 95%) | 9.5 (7.2 to 11.1) | 9.5 (5.9 to 11.5) | 9.5 (7.8 to 11.1) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Skeletal-related Event (Cohorts 4 and 5 by Cohort and Combined)

| | |
|---|---|
| End point title | Time to First Skeletal-related Event (Cohorts 4 and 5 by Cohort and Combined) |
| End point description: | |
| Time to initiation of first skeletal-related event was defined as the time from first day of study treatment to the first skeletal-related event, which was defined as radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change or antineoplastic therapy to treat bone pain. 9999 indicated that the median and/or lower or upper limit of the 95% CI was not reached due to insufficient number of participants with an event. Per protocol, analysis for this outcome measure was conducted in Cohorts 4 and 5 separately as well as combined for the first course of treatment. Analysis population was the ASaT which consisted of all allocated participants who received at least 1 dose of study treatment. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to ~52 months | |

| End point values | Cohort 4 | Cohort 5 | Cohorts 4 and 5 Combined | |
|----------------------------------|----------------------|----------------------|--------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 81 | 45 | 126 | |
| Units: Months | | | | |
| median (confidence interval 95%) | 9999 (27.6 to 9999) | 9999 (9999 to 9999) | 9999 (9999 to 9999) | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 52 months

Adverse event reporting additional description:

All-Cause Mortality included all enrolled participants. Per protocol, disease progression of cancer on study was not considered an AE unless considered related to study drug. Therefore, MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to study drug were excluded as AEs.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 24.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------------|
| Reporting group title | Cohort 1- 1st Course |
|-----------------------|----------------------|

Reporting group description:

Participants with PD-L1-positive, measurable disease received pembrolizumab 200 mg via IV infusion on Day 1 of every 3-week cycle for up to 2 years.

| | |
|-----------------------|----------------------|
| Reporting group title | Cohort 2- 1st Course |
|-----------------------|----------------------|

Reporting group description:

Participants with PD-L1 negative, measurable disease received pembrolizumab 200 mg via IV infusion on Day 1 of every 3-week cycle for up to 2 years.

| | |
|-----------------------|-----------------------|
| Reporting group title | Cohort 5 - 1st Course |
|-----------------------|-----------------------|

Reporting group description:

Participants with bone metastases only or bone-predominant disease received pembrolizumab 200 mg via IV infusion on Day 1 of every 3-week cycle.

| | |
|-----------------------|-----------------------|
| Reporting group title | Cohort 4 - 1st Course |
|-----------------------|-----------------------|

Reporting group description:

Participants with RECIST 1.1-measurable disease received pembrolizumab 200 mg via IV infusion on Day 1 of every 3-week cycle for up to 2 years.

| | |
|-----------------------|----------------------|
| Reporting group title | Cohort 1- 2nd Course |
|-----------------------|----------------------|

Reporting group description:

Eligible participants who stopped the initial course of pembrolizumab with Stable Disease (SD) or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab for up to 17 cycles (up to approximately 1 additional year) at the investigator's discretion.

| | |
|-----------------------|----------------------|
| Reporting group title | Cohort 3- 1st Course |
|-----------------------|----------------------|

Reporting group description:

Participants with bone metastases and non-measurable disease received pembrolizumab 200 mg via IV infusion on Day 1 of every 3-week cycle for up to 2 years.

| Serious adverse events | Cohort 1- 1st Course | Cohort 2- 1st Course | Cohort 5 - 1st Course |
|---|----------------------|----------------------|-----------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 70 / 133 (52.63%) | 28 / 67 (41.79%) | 19 / 45 (42.22%) |
| number of deaths (all causes) | 126 | 63 | 40 |
| number of deaths resulting from adverse events | 1 | 1 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |

| | | | |
|--|-------------------|-----------------|----------------|
| Cancer pain | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 1 / 67 (1.49%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 24 / 133 (18.05%) | 8 / 67 (11.94%) | 4 / 45 (8.89%) |
| occurrences causally related to treatment / all | 0 / 24 | 0 / 8 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 21 | 0 / 7 | 0 / 0 |
| Tumour pain | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 1 / 67 (1.49%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 1 / 67 (1.49%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malaise | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Death | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 3 / 67 (4.48%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 3 | 0 / 0 |

| | | | |
|---|-----------------|----------------|----------------|
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 1 / 67 (1.49%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 0 / 45 (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 |
| Physical deconditioning | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoxia | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 133 (0.00%) | 1 / 67 (1.49%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 2 / 133 (1.50%) | 1 / 67 (1.49%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 2 / 133 (1.50%) | 0 / 67 (0.00%) | 0 / 45 (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 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Disorientation | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 0 / 45 (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 | 0 / 133 (0.00%) | 1 / 67 (1.49%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 0 / 45 (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 |
| Aspartate aminotransferase | | | |

| | | | |
|---|-----------------|----------------|----------------|
| increased | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 0 / 45 (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 |
| Clostridium test positive | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 0 / 45 (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 | | | |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femoral neck fracture | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 0 / 45 (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 |
| Ankle fracture | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract stoma complication | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 0 / 45 (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 |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 0 / 45 (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 |
| Infusion related reaction | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 1 / 67 (1.49%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|----------------|----------------|
| Congenital, familial and genetic disorders | | | |
| Cataract congenital | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 0 / 45 (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 disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 0 / 45 (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 / 133 (0.00%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocarditis | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 0 / 45 (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 |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 0 / 45 (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 |

| | | | |
|---|-----------------|----------------|----------------|
| Tachycardia | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stress cardiomyopathy | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 1 / 45 (2.22%) |
| 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 | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 0 / 45 (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 |
| Coordination abnormal | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Depressed level of consciousness | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 0 / 45 (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 |
| Encephalopathy | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myasthenia gravis | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Miller Fisher syndrome | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subdural hygroma | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal cord compression | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 0 / 45 (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 |
| Seizure like phenomena | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Toxic encephalopathy | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 1 / 67 (1.49%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 133 (1.50%) | 0 / 67 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancytopenia | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 0 / 45 (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 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 0 / 45 (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 |
| Eye disorders | | | |
| Blindness | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 1 / 67 (1.49%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 2 / 133 (1.50%) | 1 / 67 (1.49%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|----------------|----------------|
| Constipation | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 1 / 67 (1.49%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enterocolitis | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea haemorrhagic | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 0 / 45 (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 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 1 / 67 (1.49%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Faecaloma | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 1 / 67 (1.49%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematemesis | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 0 / 45 (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 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 0 / 45 (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 |
| Inguinal hernia | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 0 / 45 (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 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestinal obstruction | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 0 / 45 (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 |
| Vomiting | | | |
| subjects affected / exposed | 3 / 133 (2.26%) | 1 / 67 (1.49%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subileus | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 0 / 45 (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 |
| Hepatobiliary disorders | | | |
| Cholangitis acute | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 0 / 45 (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 |
| Hepatic pain | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 0 / 45 (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 | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 0 / 45 (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 |
| Immune-mediated hepatitis | | | |

| | | | |
|---|------------------|----------------|----------------|
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Jaundice cholestatic | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 0 / 45 (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 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rash | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 10 / 133 (7.52%) | 2 / 67 (2.99%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 2 / 10 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bladder perforation | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Glomerulosclerosis | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 0 / 45 (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 |
| Haematuria | | | |
| subjects affected / exposed | 5 / 133 (3.76%) | 1 / 67 (1.49%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydronephrosis | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 2 / 133 (1.50%) | 0 / 67 (0.00%) | 0 / 45 (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 |
| Perinephric collection | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 1 / 67 (1.49%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 1 / 67 (1.49%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract obstruction | | | |
| subjects affected / exposed | 2 / 133 (1.50%) | 1 / 67 (1.49%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypophysitis | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 1 / 67 (1.49%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypopituitarism | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypothyroidism | | | |

| | | | |
|--|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 0 / 45 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 0 / 45 (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 |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myositis | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 0 / 45 (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 |
| Candida infection | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 1 / 67 (1.49%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|----------------|----------------|
| Clostridium difficile infection | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 0 / 45 (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 |
| Device related bacteraemia | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 0 / 45 (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 |
| Endocarditis | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 1 / 67 (1.49%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enterocolitis infectious | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 0 / 45 (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 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis norovirus | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 2 / 133 (1.50%) | 0 / 67 (0.00%) | 0 / 45 (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 |
| Necrotising fasciitis | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pelvic infection | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 0 / 45 (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 |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 0 / 45 (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 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 1 / 45 (2.22%) |
| 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 | 3 / 133 (2.26%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 1 / 67 (1.49%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 4 / 133 (3.01%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 3 / 6 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 0 / 45 (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 |
| Skin infection | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 0 / 45 (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 |
| Thrombophlebitis septic | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ureteritis | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 1 / 67 (1.49%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 7 / 133 (5.26%) | 3 / 67 (4.48%) | 3 / 45 (6.67%) |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 3 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular device infection | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Cachexia | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 1 / 45 (2.22%) |
| 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 | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dehydration | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 1 / 67 (1.49%) | 2 / 45 (4.44%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 0 / 45 (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 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 1 / 67 (1.49%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 2 / 67 (2.99%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 1 / 67 (1.49%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour lysis syndrome | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Type 1 diabetes mellitus | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Cohort 4 - 1st Course | Cohort 1- 2nd Course | Cohort 3- 1st Course |
|---|-----------------------|----------------------|----------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 26 / 81 (32.10%) | 0 / 1 (0.00%) | 25 / 58 (43.10%) |
| number of deaths (all causes) | 76 | 0 | 57 |
| number of deaths resulting from adverse events | 2 | 0 | 1 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cancer pain | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 5 / 81 (6.17%) | 0 / 1 (0.00%) | 7 / 58 (12.07%) |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 0 | 0 / 7 |
| deaths causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 4 |
| Tumour pain | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |

| | | | |
|---|----------------|---------------|----------------|
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malaise | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Death | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 1 (0.00%) | 0 / 58 (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 |
| Pain | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Physical deconditioning | | | |

| | | | |
|---|----------------|---------------|----------------|
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 1 (0.00%) | 0 / 58 (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 |
| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |

| | | | |
|---|----------------|---------------|----------------|
| Psychiatric disorders | | | |
| Disorientation | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Delirium | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium test positive | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ankle fracture | | | |

| | | | |
|---|----------------|---------------|----------------|
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract stoma complication | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infusion related reaction | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Congenital, familial and genetic disorders | | | |
| Cataract congenital | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|---------------|----------------|
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 3 / 58 (5.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocarditis | | | |
| subjects affected / exposed | 2 / 81 (2.47%) | 0 / 1 (0.00%) | 0 / 58 (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 |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stress cardiomyopathy | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 2 / 58 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Coordination abnormal | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 1 (0.00%) | 0 / 58 (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 |
| Depressed level of consciousness | | | |

| | | | |
|---|----------------|---------------|----------------|
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalopathy | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 1 (0.00%) | 0 / 58 (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 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myasthenia gravis | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 1 (0.00%) | 0 / 58 (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 |
| Miller Fisher syndrome | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 1 (0.00%) | 0 / 58 (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 |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subdural hygroma | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Spinal cord compression | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 1 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure like phenomena | | | |

| | | | |
|---|----------------|---------------|----------------|
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Toxic encephalopathy | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 81 (2.47%) | 0 / 1 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 1 (0.00%) | 0 / 58 (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 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |

| | | | |
|---|----------------|---------------|----------------|
| Blindness | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 1 (0.00%) | 0 / 58 (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 |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 81 (2.47%) | 0 / 1 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enterocolitis | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea haemorrhagic | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrooesophageal reflux disease | | | |

| | | | |
|---|----------------|---------------|----------------|
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Faecaloma | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematemesis | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 1 (0.00%) | 0 / 58 (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 |
| Large intestinal obstruction | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subileus | | | |

| | | | |
|---|----------------|---------------|----------------|
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholangitis acute | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic pain | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune-mediated hepatitis | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 1 (0.00%) | 0 / 58 (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 |
| Jaundice cholestatic | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 1 (0.00%) | 0 / 58 (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 |
| Rash | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 1 (0.00%) | 0 / 58 (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 |
| Renal and urinary disorders | | | |

| | | | |
|---|----------------|---------------|----------------|
| Acute kidney injury | | | |
| subjects affected / exposed | 2 / 81 (2.47%) | 0 / 1 (0.00%) | 0 / 58 (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 |
| Bladder perforation | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 1 (0.00%) | 0 / 58 (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 |
| Glomerulosclerosis | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematuria | | | |
| subjects affected / exposed | 2 / 81 (2.47%) | 0 / 1 (0.00%) | 0 / 58 (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 |
| Hydronephrosis | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Perinephric collection | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract obstruction | | | |

| | | | |
|---|----------------|---------------|----------------|
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 1 (0.00%) | 0 / 58 (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 |
| Endocrine disorders | | | |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 2 / 81 (2.47%) | 0 / 1 (0.00%) | 0 / 58 (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 |
| Hypophysitis | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypopituitarism | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 1 (0.00%) | 0 / 58 (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 |
| Hypothyroidism | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myositis | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 1 (0.00%) | 0 / 58 (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 Appendicitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 81 (0.00%) 0 / 0 0 / 0 | 0 / 1 (0.00%) 0 / 0 0 / 0 | 0 / 58 (0.00%) 0 / 0 0 / 0 |
| Bronchitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 81 (0.00%) 0 / 0 0 / 0 | 0 / 1 (0.00%) 0 / 0 0 / 0 | 0 / 58 (0.00%) 0 / 0 0 / 0 |
| Candida infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 81 (0.00%) 0 / 0 0 / 0 | 0 / 1 (0.00%) 0 / 0 0 / 0 | 0 / 58 (0.00%) 0 / 0 0 / 0 |
| Cellulitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 81 (0.00%) 0 / 0 0 / 0 | 0 / 1 (0.00%) 0 / 0 0 / 0 | 0 / 58 (0.00%) 0 / 0 0 / 0 |
| Clostridium difficile infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 81 (1.23%) 0 / 1 0 / 0 | 0 / 1 (0.00%) 0 / 0 0 / 0 | 0 / 58 (0.00%) 0 / 0 0 / 0 |
| Device related bacteraemia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 81 (0.00%) 0 / 0 0 / 0 | 0 / 1 (0.00%) 0 / 0 0 / 0 | 0 / 58 (0.00%) 0 / 0 0 / 0 |
| Endocarditis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 81 (0.00%) 0 / 0 0 / 0 | 0 / 1 (0.00%) 0 / 0 0 / 0 | 0 / 58 (0.00%) 0 / 0 0 / 0 |
| Enterocolitis infectious subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 81 (0.00%) 0 / 0 0 / 0 | 0 / 1 (0.00%) 0 / 0 0 / 0 | 0 / 58 (0.00%) 0 / 0 0 / 0 |
| Gastroenteritis | | | |

| | | | |
|---|----------------|---------------|----------------|
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 2 / 58 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis norovirus | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 1 (0.00%) | 0 / 58 (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 |
| Influenza | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 1 (0.00%) | 0 / 58 (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 |
| Necrotising fasciitis | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pelvic infection | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |

| | | | |
|---|----------------|---------------|----------------|
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 1 (0.00%) | 2 / 58 (3.45%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 1 (0.00%) | 0 / 58 (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 |
| Septic shock | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin infection | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombophlebitis septic | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 1 (0.00%) | 0 / 58 (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 |
| Ureteritis | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |

| | | | |
|---|----------------|---------------|----------------|
| subjects affected / exposed | 2 / 81 (2.47%) | 0 / 1 (0.00%) | 3 / 58 (5.17%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular device infection | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Cachexia | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 2 / 81 (2.47%) | 0 / 1 (0.00%) | 0 / 58 (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 |
| Dehydration | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 1 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypocalcaemia | | | |

| | | | |
|---|----------------|---------------|----------------|
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour lysis syndrome | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 1 (0.00%) | 0 / 58 (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 |
| Type 1 diabetes mellitus | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Cohort 1- 1st Course | Cohort 2- 1st Course | Cohort 5 - 1st Course |
|--|----------------------|----------------------|-----------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 128 / 133 (96.24%) | 62 / 67 (92.54%) | 42 / 45 (93.33%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cancer pain | | | |
| subjects affected / exposed | 3 / 133 (2.26%) | 4 / 67 (5.97%) | 0 / 45 (0.00%) |
| occurrences (all) | 4 | 5 | 0 |
| Vascular disorders | | | |

| | | | |
|--|-------------------|------------------|------------------|
| Hot flush | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 1 / 67 (1.49%) | 2 / 45 (4.44%) |
| occurrences (all) | 1 | 1 | 2 |
| Hypertension | | | |
| subjects affected / exposed | 6 / 133 (4.51%) | 0 / 67 (0.00%) | 4 / 45 (8.89%) |
| occurrences (all) | 9 | 0 | 4 |
| Hypotension | | | |
| subjects affected / exposed | 7 / 133 (5.26%) | 1 / 67 (1.49%) | 1 / 45 (2.22%) |
| occurrences (all) | 7 | 1 | 1 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 18 / 133 (13.53%) | 11 / 67 (16.42%) | 5 / 45 (11.11%) |
| occurrences (all) | 20 | 11 | 5 |
| Chest pain | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 1 / 67 (1.49%) | 2 / 45 (4.44%) |
| occurrences (all) | 1 | 1 | 2 |
| Chills | | | |
| subjects affected / exposed | 7 / 133 (5.26%) | 5 / 67 (7.46%) | 1 / 45 (2.22%) |
| occurrences (all) | 7 | 5 | 1 |
| Fatigue | | | |
| subjects affected / exposed | 39 / 133 (29.32%) | 22 / 67 (32.84%) | 18 / 45 (40.00%) |
| occurrences (all) | 41 | 22 | 19 |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 3 / 45 (6.67%) |
| occurrences (all) | 0 | 0 | 3 |
| Influenza like illness | | | |
| subjects affected / exposed | 4 / 133 (3.01%) | 2 / 67 (2.99%) | 7 / 45 (15.56%) |
| occurrences (all) | 5 | 2 | 7 |
| Malaise | | | |
| subjects affected / exposed | 2 / 133 (1.50%) | 4 / 67 (5.97%) | 1 / 45 (2.22%) |
| occurrences (all) | 2 | 5 | 1 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 2 / 133 (1.50%) | 2 / 67 (2.99%) | 2 / 45 (4.44%) |
| occurrences (all) | 2 | 2 | 3 |
| Pain | | | |

| | | | |
|--|-------------------------|------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 4 / 133 (3.01%) 4 | 2 / 67 (2.99%) 2 | 1 / 45 (2.22%) 1 |
| Oedema peripheral subjects affected / exposed occurrences (all) | 21 / 133 (15.79%) 24 | 7 / 67 (10.45%) 8 | 3 / 45 (6.67%) 4 |
| Swelling face subjects affected / exposed occurrences (all) | 1 / 133 (0.75%) 1 | 0 / 67 (0.00%) 0 | 3 / 45 (6.67%) 3 |
| Pyrexia subjects affected / exposed occurrences (all) | 13 / 133 (9.77%) 14 | 11 / 67 (16.42%) 13 | 3 / 45 (6.67%) 3 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough subjects affected / exposed occurrences (all) | 14 / 133 (10.53%) 18 | 10 / 67 (14.93%) 11 | 5 / 45 (11.11%) 5 |
| Dyspnoea subjects affected / exposed occurrences (all) | 17 / 133 (12.78%) 18 | 6 / 67 (8.96%) 6 | 11 / 45 (24.44%) 12 |
| Nasal congestion subjects affected / exposed occurrences (all) | 3 / 133 (2.26%) 3 | 0 / 67 (0.00%) 0 | 2 / 45 (4.44%) 2 |
| Psychiatric disorders | | | |
| Anxiety subjects affected / exposed occurrences (all) | 1 / 133 (0.75%) 1 | 5 / 67 (7.46%) 5 | 1 / 45 (2.22%) 1 |
| Depression subjects affected / exposed occurrences (all) | 2 / 133 (1.50%) 2 | 1 / 67 (1.49%) 1 | 4 / 45 (8.89%) 4 |
| Insomnia subjects affected / exposed occurrences (all) | 8 / 133 (6.02%) 9 | 4 / 67 (5.97%) 4 | 1 / 45 (2.22%) 1 |
| Investigations | | | |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 7 / 133 (5.26%) 7 | 1 / 67 (1.49%) 1 | 2 / 45 (4.44%) 2 |
| Aspartate aminotransferase increased | | | |

| | | | |
|--|-------------------|----------------|-----------------|
| subjects affected / exposed | 11 / 133 (8.27%) | 6 / 67 (8.96%) | 2 / 45 (4.44%) |
| occurrences (all) | 11 | 6 | 2 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 2 / 67 (2.99%) | 4 / 45 (8.89%) |
| occurrences (all) | 1 | 2 | 4 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 8 / 133 (6.02%) | 5 / 67 (7.46%) | 4 / 45 (8.89%) |
| occurrences (all) | 8 | 5 | 4 |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 2 / 133 (1.50%) | 0 / 67 (0.00%) | 1 / 45 (2.22%) |
| occurrences (all) | 3 | 0 | 1 |
| Weight decreased | | | |
| subjects affected / exposed | 16 / 133 (12.03%) | 6 / 67 (8.96%) | 5 / 45 (11.11%) |
| occurrences (all) | 17 | 6 | 5 |
| Platelet count decreased | | | |
| subjects affected / exposed | 2 / 133 (1.50%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 6 / 133 (4.51%) | 1 / 67 (1.49%) | 5 / 45 (11.11%) |
| occurrences (all) | 6 | 1 | 10 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 7 / 133 (5.26%) | 3 / 67 (4.48%) | 5 / 45 (11.11%) |
| occurrences (all) | 7 | 3 | 6 |
| Dysgeusia | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 3 / 67 (4.48%) | 4 / 45 (8.89%) |
| occurrences (all) | 1 | 3 | 4 |
| Memory impairment | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 3 / 45 (6.67%) |
| occurrences (all) | 0 | 0 | 3 |
| Headache | | | |
| subjects affected / exposed | 9 / 133 (6.77%) | 5 / 67 (7.46%) | 6 / 45 (13.33%) |
| occurrences (all) | 10 | 7 | 6 |
| Blood and lymphatic system disorders | | | |

| | | | |
|---|-------------------------|------------------------|------------------------|
| Anaemia subjects affected / exposed occurrences (all) | 35 / 133 (26.32%) 39 | 12 / 67 (17.91%) 12 | 6 / 45 (13.33%) 6 |
| Gastrointestinal disorders | | | |
| Abdominal pain subjects affected / exposed occurrences (all) | 14 / 133 (10.53%) 15 | 7 / 67 (10.45%) 7 | 2 / 45 (4.44%) 2 |
| Constipation subjects affected / exposed occurrences (all) | 25 / 133 (18.80%) 27 | 21 / 67 (31.34%) 23 | 8 / 45 (17.78%) 8 |
| Dysphagia subjects affected / exposed occurrences (all) | 1 / 133 (0.75%) 1 | 1 / 67 (1.49%) 1 | 1 / 45 (2.22%) 1 |
| Dry mouth subjects affected / exposed occurrences (all) | 7 / 133 (5.26%) 7 | 6 / 67 (8.96%) 6 | 2 / 45 (4.44%) 2 |
| Diarrhoea subjects affected / exposed occurrences (all) | 28 / 133 (21.05%) 35 | 17 / 67 (25.37%) 25 | 11 / 45 (24.44%) 15 |
| Nausea subjects affected / exposed occurrences (all) | 37 / 133 (27.82%) 45 | 26 / 67 (38.81%) 31 | 8 / 45 (17.78%) 9 |
| Vomiting subjects affected / exposed occurrences (all) | 17 / 133 (12.78%) 22 | 18 / 67 (26.87%) 24 | 4 / 45 (8.89%) 4 |
| Skin and subcutaneous tissue disorders | | | |
| Dry skin subjects affected / exposed occurrences (all) | 7 / 133 (5.26%) 7 | 1 / 67 (1.49%) 1 | 3 / 45 (6.67%) 3 |
| Pruritus subjects affected / exposed occurrences (all) | 14 / 133 (10.53%) 16 | 4 / 67 (5.97%) 4 | 4 / 45 (8.89%) 4 |
| Rash maculo-papular subjects affected / exposed occurrences (all) | 3 / 133 (2.26%) 5 | 2 / 67 (2.99%) 2 | 4 / 45 (8.89%) 5 |
| Rash | | | |

| | | | |
|--|----------------------|---------------------|----------------------|
| subjects affected / exposed occurrences (all) | 7 / 133 (5.26%) 8 | 3 / 67 (4.48%) 3 | 6 / 45 (13.33%) 6 |
| Renal and urinary disorders | | | |
| Micturition urgency | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 67 (0.00%) | 3 / 45 (6.67%) |
| occurrences (all) | 0 | 0 | 3 |
| Haematuria | | | |
| subjects affected / exposed | 10 / 133 (7.52%) | 3 / 67 (4.48%) | 6 / 45 (13.33%) |
| occurrences (all) | 18 | 3 | 7 |
| Dysuria | | | |
| subjects affected / exposed | 4 / 133 (3.01%) | 2 / 67 (2.99%) | 3 / 45 (6.67%) |
| occurrences (all) | 4 | 2 | 3 |
| Nocturia | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 1 / 67 (1.49%) | 3 / 45 (6.67%) |
| occurrences (all) | 1 | 1 | 3 |
| Proteinuria | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 67 (0.00%) | 2 / 45 (4.44%) |
| occurrences (all) | 3 | 0 | 3 |
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 5 / 133 (3.76%) | 1 / 67 (1.49%) | 8 / 45 (17.78%) |
| occurrences (all) | 5 | 1 | 8 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 26 / 133 (19.55%) | 11 / 67 (16.42%) | 8 / 45 (17.78%) |
| occurrences (all) | 30 | 11 | 10 |
| Back pain | | | |
| subjects affected / exposed | 17 / 133 (12.78%) | 11 / 67 (16.42%) | 15 / 45 (33.33%) |
| occurrences (all) | 23 | 12 | 19 |
| Bone pain | | | |
| subjects affected / exposed | 6 / 133 (4.51%) | 5 / 67 (7.46%) | 4 / 45 (8.89%) |
| occurrences (all) | 8 | 5 | 5 |
| Flank pain | | | |
| subjects affected / exposed | 4 / 133 (3.01%) | 1 / 67 (1.49%) | 3 / 45 (6.67%) |
| occurrences (all) | 4 | 1 | 3 |
| Musculoskeletal pain | | | |

| | | | |
|------------------------------------|-------------------|------------------|------------------|
| subjects affected / exposed | 2 / 133 (1.50%) | 0 / 67 (0.00%) | 2 / 45 (4.44%) |
| occurrences (all) | 2 | 0 | 2 |
| Muscular weakness | | | |
| subjects affected / exposed | 7 / 133 (5.26%) | 1 / 67 (1.49%) | 3 / 45 (6.67%) |
| occurrences (all) | 8 | 1 | 3 |
| Myalgia | | | |
| subjects affected / exposed | 6 / 133 (4.51%) | 4 / 67 (5.97%) | 3 / 45 (6.67%) |
| occurrences (all) | 7 | 4 | 3 |
| Pain in extremity | | | |
| subjects affected / exposed | 12 / 133 (9.02%) | 7 / 67 (10.45%) | 7 / 45 (15.56%) |
| occurrences (all) | 13 | 7 | 8 |
| Muscle spasms | | | |
| subjects affected / exposed | 2 / 133 (1.50%) | 0 / 67 (0.00%) | 2 / 45 (4.44%) |
| occurrences (all) | 2 | 0 | 2 |
| Infections and infestations | | | |
| Cystitis | | | |
| subjects affected / exposed | 3 / 133 (2.26%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 133 (1.50%) | 0 / 67 (0.00%) | 2 / 45 (4.44%) |
| occurrences (all) | 2 | 0 | 2 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 5 / 133 (3.76%) | 1 / 67 (1.49%) | 3 / 45 (6.67%) |
| occurrences (all) | 7 | 1 | 3 |
| Urinary tract infection | | | |
| subjects affected / exposed | 10 / 133 (7.52%) | 5 / 67 (7.46%) | 3 / 45 (6.67%) |
| occurrences (all) | 14 | 6 | 6 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 38 / 133 (28.57%) | 23 / 67 (34.33%) | 11 / 45 (24.44%) |
| occurrences (all) | 44 | 25 | 13 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 6 / 133 (4.51%) | 2 / 67 (2.99%) | 2 / 45 (4.44%) |
| occurrences (all) | 6 | 2 | 2 |
| Hypocalcaemia | | | |

| | | | |
|-----------------------------|-----------------|----------------|----------------|
| subjects affected / exposed | 3 / 133 (2.26%) | 0 / 67 (0.00%) | 0 / 45 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 4 / 133 (3.01%) | 1 / 67 (1.49%) | 3 / 45 (6.67%) |
| occurrences (all) | 6 | 1 | 4 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 4 / 133 (3.01%) | 0 / 67 (0.00%) | 1 / 45 (2.22%) |
| occurrences (all) | 5 | 0 | 1 |
| Hyponatraemia | | | |
| subjects affected / exposed | 8 / 133 (6.02%) | 4 / 67 (5.97%) | 2 / 45 (4.44%) |
| occurrences (all) | 9 | 4 | 2 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 8 / 133 (6.02%) | 1 / 67 (1.49%) | 1 / 45 (2.22%) |
| occurrences (all) | 10 | 1 | 1 |

| Non-serious adverse events | Cohort 4 - 1st Course | Cohort 1- 2nd Course | Cohort 3- 1st Course |
|---|-----------------------|----------------------|----------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 79 / 81 (97.53%) | 1 / 1 (100.00%) | 57 / 58 (98.28%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cancer pain | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 2 / 58 (3.45%) |
| occurrences (all) | 0 | 0 | 2 |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 6 / 81 (7.41%) | 0 / 1 (0.00%) | 2 / 58 (3.45%) |
| occurrences (all) | 7 | 0 | 2 |
| Hypertension | | | |
| subjects affected / exposed | 9 / 81 (11.11%) | 0 / 1 (0.00%) | 3 / 58 (5.17%) |
| occurrences (all) | 9 | 0 | 4 |
| Hypotension | | | |
| subjects affected / exposed | 2 / 81 (2.47%) | 0 / 1 (0.00%) | 1 / 58 (1.72%) |
| occurrences (all) | 2 | 0 | 1 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 9 / 81 (11.11%) | 1 / 1 (100.00%) | 12 / 58 (20.69%) |
| occurrences (all) | 9 | 1 | 14 |

| | | | |
|---|------------------|---------------|------------------|
| Chest pain | | | |
| subjects affected / exposed | 2 / 81 (2.47%) | 0 / 1 (0.00%) | 3 / 58 (5.17%) |
| occurrences (all) | 2 | 0 | 3 |
| Chills | | | |
| subjects affected / exposed | 3 / 81 (3.70%) | 0 / 1 (0.00%) | 1 / 58 (1.72%) |
| occurrences (all) | 4 | 0 | 4 |
| Fatigue | | | |
| subjects affected / exposed | 36 / 81 (44.44%) | 0 / 1 (0.00%) | 18 / 58 (31.03%) |
| occurrences (all) | 42 | 0 | 18 |
| Gait disturbance | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 2 / 81 (2.47%) | 0 / 1 (0.00%) | 4 / 58 (6.90%) |
| occurrences (all) | 2 | 0 | 4 |
| Malaise | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 1 (0.00%) | 3 / 58 (5.17%) |
| occurrences (all) | 1 | 0 | 3 |
| Pain | | | |
| subjects affected / exposed | 6 / 81 (7.41%) | 0 / 1 (0.00%) | 1 / 58 (1.72%) |
| occurrences (all) | 6 | 0 | 1 |
| Oedema peripheral | | | |
| subjects affected / exposed | 8 / 81 (9.88%) | 0 / 1 (0.00%) | 5 / 58 (8.62%) |
| occurrences (all) | 12 | 0 | 6 |
| Swelling face | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 5 / 81 (6.17%) | 0 / 1 (0.00%) | 3 / 58 (5.17%) |
| occurrences (all) | 5 | 0 | 4 |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|--------------------------------------|------------------|-----------------|-----------------|
| Cough | | | |
| subjects affected / exposed | 14 / 81 (17.28%) | 1 / 1 (100.00%) | 4 / 58 (6.90%) |
| occurrences (all) | 14 | 1 | 4 |
| Dyspnoea | | | |
| subjects affected / exposed | 11 / 81 (13.58%) | 0 / 1 (0.00%) | 4 / 58 (6.90%) |
| occurrences (all) | 11 | 0 | 4 |
| Nasal congestion | | | |
| subjects affected / exposed | 5 / 81 (6.17%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 3 / 58 (5.17%) |
| occurrences (all) | 0 | 0 | 3 |
| Depression | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 1 (0.00%) | 4 / 58 (6.90%) |
| occurrences (all) | 1 | 0 | 4 |
| Insomnia | | | |
| subjects affected / exposed | 5 / 81 (6.17%) | 0 / 1 (0.00%) | 5 / 58 (8.62%) |
| occurrences (all) | 5 | 0 | 6 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 2 / 81 (2.47%) | 0 / 1 (0.00%) | 6 / 58 (10.34%) |
| occurrences (all) | 2 | 0 | 6 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 1 (0.00%) | 6 / 58 (10.34%) |
| occurrences (all) | 1 | 0 | 7 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 3 / 81 (3.70%) | 0 / 1 (0.00%) | 4 / 58 (6.90%) |
| occurrences (all) | 5 | 0 | 4 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 2 / 81 (2.47%) | 0 / 1 (0.00%) | 4 / 58 (6.90%) |
| occurrences (all) | 3 | 0 | 4 |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 6 / 81 (7.41%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 11 | 0 | 0 |
| Weight decreased | | | |

| | | | |
|--|------------------------|----------------------|------------------------|
| subjects affected / exposed occurrences (all) | 14 / 81 (17.28%) 15 | 0 / 1 (0.00%) 0 | 9 / 58 (15.52%) 9 |
| Platelet count decreased subjects affected / exposed occurrences (all) | 2 / 81 (2.47%) 2 | 0 / 1 (0.00%) 0 | 4 / 58 (6.90%) 6 |
| Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all) | 12 / 81 (14.81%) 15 | 0 / 1 (0.00%) 0 | 1 / 58 (1.72%) 1 |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 8 / 81 (9.88%) 14 | 0 / 1 (0.00%) 0 | 3 / 58 (5.17%) 3 |
| Dysgeusia subjects affected / exposed occurrences (all) | 6 / 81 (7.41%) 7 | 0 / 1 (0.00%) 0 | 4 / 58 (6.90%) 4 |
| Memory impairment subjects affected / exposed occurrences (all) | 1 / 81 (1.23%) 1 | 0 / 1 (0.00%) 0 | 0 / 58 (0.00%) 0 |
| Headache subjects affected / exposed occurrences (all) | 5 / 81 (6.17%) 6 | 0 / 1 (0.00%) 0 | 5 / 58 (8.62%) 6 |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 11 / 81 (13.58%) 13 | 0 / 1 (0.00%) 0 | 21 / 58 (36.21%) 24 |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) | 6 / 81 (7.41%) 6 | 0 / 1 (0.00%) 0 | 1 / 58 (1.72%) 1 |
| Constipation subjects affected / exposed occurrences (all) | 12 / 81 (14.81%) 13 | 1 / 1 (100.00%) 1 | 13 / 58 (22.41%) 15 |
| Dysphagia subjects affected / exposed occurrences (all) | 1 / 81 (1.23%) 1 | 0 / 1 (0.00%) 0 | 3 / 58 (5.17%) 3 |

| | | | |
|---|------------------------|----------------------|------------------------|
| Dry mouth subjects affected / exposed occurrences (all) | 9 / 81 (11.11%) 9 | 0 / 1 (0.00%) 0 | 1 / 58 (1.72%) 1 |
| Diarrhoea subjects affected / exposed occurrences (all) | 24 / 81 (29.63%) 27 | 1 / 1 (100.00%) 1 | 10 / 58 (17.24%) 12 |
| Nausea subjects affected / exposed occurrences (all) | 19 / 81 (23.46%) 21 | 0 / 1 (0.00%) 0 | 13 / 58 (22.41%) 15 |
| Vomiting subjects affected / exposed occurrences (all) | 5 / 81 (6.17%) 5 | 1 / 1 (100.00%) 1 | 4 / 58 (6.90%) 4 |
| Skin and subcutaneous tissue disorders | | | |
| Dry skin subjects affected / exposed occurrences (all) | 7 / 81 (8.64%) 7 | 0 / 1 (0.00%) 0 | 0 / 58 (0.00%) 0 |
| Pruritus subjects affected / exposed occurrences (all) | 16 / 81 (19.75%) 16 | 1 / 1 (100.00%) 1 | 7 / 58 (12.07%) 7 |
| Rash maculo-papular subjects affected / exposed occurrences (all) | 9 / 81 (11.11%) 10 | 0 / 1 (0.00%) 0 | 1 / 58 (1.72%) 1 |
| Rash subjects affected / exposed occurrences (all) | 19 / 81 (23.46%) 25 | 0 / 1 (0.00%) 0 | 1 / 58 (1.72%) 1 |
| Renal and urinary disorders | | | |
| Micturition urgency subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 0 / 1 (0.00%) 0 | 0 / 58 (0.00%) 0 |
| Haematuria subjects affected / exposed occurrences (all) | 9 / 81 (11.11%) 11 | 0 / 1 (0.00%) 0 | 3 / 58 (5.17%) 3 |
| Dysuria subjects affected / exposed occurrences (all) | 1 / 81 (1.23%) 1 | 0 / 1 (0.00%) 0 | 0 / 58 (0.00%) 0 |
| Nocturia | | | |

| | | | |
|---|------------------|---------------|------------------|
| subjects affected / exposed | 2 / 81 (2.47%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Proteinuria | | | |
| subjects affected / exposed | 5 / 81 (6.17%) | 0 / 1 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 6 | 0 | 0 |
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 12 / 81 (14.81%) | 0 / 1 (0.00%) | 1 / 58 (1.72%) |
| occurrences (all) | 12 | 0 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 17 / 81 (20.99%) | 0 / 1 (0.00%) | 9 / 58 (15.52%) |
| occurrences (all) | 23 | 0 | 11 |
| Back pain | | | |
| subjects affected / exposed | 19 / 81 (23.46%) | 0 / 1 (0.00%) | 13 / 58 (22.41%) |
| occurrences (all) | 20 | 0 | 15 |
| Bone pain | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 6 / 58 (10.34%) |
| occurrences (all) | 0 | 0 | 6 |
| Flank pain | | | |
| subjects affected / exposed | 4 / 81 (4.94%) | 0 / 1 (0.00%) | 1 / 58 (1.72%) |
| occurrences (all) | 4 | 0 | 1 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 1 (0.00%) | 3 / 58 (5.17%) |
| occurrences (all) | 1 | 0 | 3 |
| Muscular weakness | | | |
| subjects affected / exposed | 7 / 81 (8.64%) | 0 / 1 (0.00%) | 3 / 58 (5.17%) |
| occurrences (all) | 9 | 0 | 3 |
| Myalgia | | | |
| subjects affected / exposed | 3 / 81 (3.70%) | 0 / 1 (0.00%) | 7 / 58 (12.07%) |
| occurrences (all) | 4 | 0 | 7 |
| Pain in extremity | | | |
| subjects affected / exposed | 12 / 81 (14.81%) | 0 / 1 (0.00%) | 6 / 58 (10.34%) |
| occurrences (all) | 15 | 0 | 6 |
| Muscle spasms | | | |

| | | | |
|--|---------------------|----------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 1 / 1 (100.00%) 1 | 1 / 58 (1.72%) 1 |
| Infections and infestations | | | |
| Cystitis | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 3 / 58 (5.17%) |
| occurrences (all) | 0 | 0 | 3 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 3 / 58 (5.17%) |
| occurrences (all) | 0 | 0 | 3 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 5 / 81 (6.17%) | 0 / 1 (0.00%) | 3 / 58 (5.17%) |
| occurrences (all) | 7 | 0 | 3 |
| Urinary tract infection | | | |
| subjects affected / exposed | 6 / 81 (7.41%) | 0 / 1 (0.00%) | 7 / 58 (12.07%) |
| occurrences (all) | 7 | 0 | 8 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 19 / 81 (23.46%) | 0 / 1 (0.00%) | 19 / 58 (32.76%) |
| occurrences (all) | 23 | 0 | 22 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 7 / 81 (8.64%) | 0 / 1 (0.00%) | 2 / 58 (3.45%) |
| occurrences (all) | 12 | 0 | 2 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 0 / 1 (0.00%) | 3 / 58 (5.17%) |
| occurrences (all) | 0 | 0 | 3 |
| Hypokalaemia | | | |
| subjects affected / exposed | 2 / 81 (2.47%) | 0 / 1 (0.00%) | 4 / 58 (6.90%) |
| occurrences (all) | 2 | 0 | 8 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 2 / 81 (2.47%) | 0 / 1 (0.00%) | 3 / 58 (5.17%) |
| occurrences (all) | 2 | 0 | 3 |
| Hyponatraemia | | | |
| subjects affected / exposed | 7 / 81 (8.64%) | 0 / 1 (0.00%) | 2 / 58 (3.45%) |
| occurrences (all) | 8 | 0 | 2 |
| Hypophosphataemia | | | |

| | | | |
|-----------------------------|----------------|---------------|----------------|
| subjects affected / exposed | 2 / 81 (2.47%) | 0 / 1 (0.00%) | 4 / 58 (6.90%) |
| occurrences (all) | 3 | 0 | 4 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 16 September 2016 | Exclusion criterion # 8 was modified to include pneumonitis criteria |
| 12 April 2017 | Number of participants in Cohorts 1 and 2 updated to total 200, instead of 100 in each cohort and enrollment in Cohort 2 (PD-L1 negative participants) would not be stopped at 100 participants |
| 12 June 2017 | Added Cohorts 4 (RECIST 1.1 measurable disease) and 5 (participants with bone metastases only or bone-predominant disease) for pembrolizumab + enzalutamide |
| 02 August 2017 | Specified blood collections for pembrolizumab for Cohorts 1 through 3 and deleted collections for Cohorts 4 and 5 |
| 25 January 2018 | Deleted DOR and rPFS from immune-related RECIST (irRECIST) exploratory objective |
| 26 November 2019 | Added liquid formulation to product description |
| 23 September 2021 | Added language to state that upon trial completion, participants were discontinued and may be enrolled in a pembrolizumab extension study, if available |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported