



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
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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
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Arm title	Cohort 1: PD-L1 positive with measurable disease
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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
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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
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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
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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
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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
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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
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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
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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			
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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
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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
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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
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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
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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
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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
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Subject analysis set type	Intention-to-treat
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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
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Subject analysis set type	Intention-to-treat
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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
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Subject analysis set type	Intention-to-treat
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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
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Subject analysis set type	Intention-to-treat
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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]
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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
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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)
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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
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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
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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)
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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)
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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
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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)
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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
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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)
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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
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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)
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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
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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)
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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
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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)
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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
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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
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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:	
<p>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.</p>	
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:	
<p>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.</p>	

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)
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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
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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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.1
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Reporting groups

Reporting group title	Cohort 1- 1st Course
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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
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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
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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
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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
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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
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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
Gastroesophageal 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	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
Bronchitis			
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
Candida 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
Cellulitis			
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 difficile 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
Device related bacteraemia			
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
Endocarditis			
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
Enterocolitis infectious			
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
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 occurrences (all)	0 / 133 (0.00%) 0	0 / 67 (0.00%) 0	3 / 45 (6.67%) 3
Haematuria subjects affected / exposed occurrences (all)	10 / 133 (7.52%) 18	3 / 67 (4.48%) 3	6 / 45 (13.33%) 7
Dysuria subjects affected / exposed occurrences (all)	4 / 133 (3.01%) 4	2 / 67 (2.99%) 2	3 / 45 (6.67%) 3
Nocturia subjects affected / exposed occurrences (all)	1 / 133 (0.75%) 1	1 / 67 (1.49%) 1	3 / 45 (6.67%) 3
Proteinuria subjects affected / exposed occurrences (all)	1 / 133 (0.75%) 3	0 / 67 (0.00%) 0	2 / 45 (4.44%) 3
Endocrine disorders			
Hypothyroidism subjects affected / exposed occurrences (all)	5 / 133 (3.76%) 5	1 / 67 (1.49%) 1	8 / 45 (17.78%) 8
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	26 / 133 (19.55%) 30	11 / 67 (16.42%) 11	8 / 45 (17.78%) 10
Back pain subjects affected / exposed occurrences (all)	17 / 133 (12.78%) 23	11 / 67 (16.42%) 12	15 / 45 (33.33%) 19
Bone pain subjects affected / exposed occurrences (all)	6 / 133 (4.51%) 8	5 / 67 (7.46%) 5	4 / 45 (8.89%) 5
Flank pain subjects affected / exposed occurrences (all)	4 / 133 (3.01%) 4	1 / 67 (1.49%) 1	3 / 45 (6.67%) 3
Musculoskeletal pain			

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

subjects affected / exposed occurrences (all)	3 / 133 (2.26%) 3	0 / 67 (0.00%) 0	0 / 45 (0.00%) 0
Hypokalaemia subjects affected / exposed occurrences (all)	4 / 133 (3.01%) 6	1 / 67 (1.49%) 1	3 / 45 (6.67%) 4
Hypomagnesaemia subjects affected / exposed occurrences (all)	4 / 133 (3.01%) 5	0 / 67 (0.00%) 0	1 / 45 (2.22%) 1
Hyponatraemia subjects affected / exposed occurrences (all)	8 / 133 (6.02%) 9	4 / 67 (5.97%) 4	2 / 45 (4.44%) 2
Hypophosphataemia subjects affected / exposed occurrences (all)	8 / 133 (6.02%) 10	1 / 67 (1.49%) 1	1 / 45 (2.22%) 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 occurrences (all)	0 / 81 (0.00%) 0	0 / 1 (0.00%) 0	2 / 58 (3.45%) 2
Vascular disorders Hot flush subjects affected / exposed occurrences (all)	6 / 81 (7.41%) 7	0 / 1 (0.00%) 0	2 / 58 (3.45%) 2
Hypertension subjects affected / exposed occurrences (all)	9 / 81 (11.11%) 9	0 / 1 (0.00%) 0	3 / 58 (5.17%) 4
Hypotension subjects affected / exposed occurrences (all)	2 / 81 (2.47%) 2	0 / 1 (0.00%) 0	1 / 58 (1.72%) 1
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	9 / 81 (11.11%) 9	1 / 1 (100.00%) 1	12 / 58 (20.69%) 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 occurrences (all)	14 / 81 (17.28%) 14	1 / 1 (100.00%) 1	4 / 58 (6.90%) 4
Dyspnoea subjects affected / exposed occurrences (all)	11 / 81 (13.58%) 11	0 / 1 (0.00%) 0	4 / 58 (6.90%) 4
Nasal congestion subjects affected / exposed occurrences (all)	5 / 81 (6.17%) 5	0 / 1 (0.00%) 0	0 / 58 (0.00%) 0
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	0 / 1 (0.00%) 0	3 / 58 (5.17%) 3
Depression subjects affected / exposed occurrences (all)	1 / 81 (1.23%) 1	0 / 1 (0.00%) 0	4 / 58 (6.90%) 4
Insomnia subjects affected / exposed occurrences (all)	5 / 81 (6.17%) 5	0 / 1 (0.00%) 0	5 / 58 (8.62%) 6
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	2 / 81 (2.47%) 2	0 / 1 (0.00%) 0	6 / 58 (10.34%) 6
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	1 / 81 (1.23%) 1	0 / 1 (0.00%) 0	6 / 58 (10.34%) 7
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	3 / 81 (3.70%) 5	0 / 1 (0.00%) 0	4 / 58 (6.90%) 4
Blood creatinine increased subjects affected / exposed occurrences (all)	2 / 81 (2.47%) 3	0 / 1 (0.00%) 0	4 / 58 (6.90%) 4
Lymphocyte count decreased subjects affected / exposed occurrences (all)	6 / 81 (7.41%) 11	0 / 1 (0.00%) 0	0 / 58 (0.00%) 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 occurrences (all)	2 / 81 (2.47%) 2	0 / 1 (0.00%) 0	0 / 58 (0.00%) 0
Proteinuria subjects affected / exposed occurrences (all)	5 / 81 (6.17%) 6	0 / 1 (0.00%) 0	0 / 58 (0.00%) 0
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	12 / 81 (14.81%) 12	0 / 1 (0.00%) 0	1 / 58 (1.72%) 1
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	17 / 81 (20.99%) 23	0 / 1 (0.00%) 0	9 / 58 (15.52%) 11
Back pain subjects affected / exposed occurrences (all)	19 / 81 (23.46%) 20	0 / 1 (0.00%) 0	13 / 58 (22.41%) 15
Bone pain subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	0 / 1 (0.00%) 0	6 / 58 (10.34%) 6
Flank pain subjects affected / exposed occurrences (all)	4 / 81 (4.94%) 4	0 / 1 (0.00%) 0	1 / 58 (1.72%) 1
Musculoskeletal pain subjects affected / exposed occurrences (all)	1 / 81 (1.23%) 1	0 / 1 (0.00%) 0	3 / 58 (5.17%) 3
Muscular weakness subjects affected / exposed occurrences (all)	7 / 81 (8.64%) 9	0 / 1 (0.00%) 0	3 / 58 (5.17%) 3
Myalgia subjects affected / exposed occurrences (all)	3 / 81 (3.70%) 4	0 / 1 (0.00%) 0	7 / 58 (12.07%) 7
Pain in extremity subjects affected / exposed occurrences (all)	12 / 81 (14.81%) 15	0 / 1 (0.00%) 0	6 / 58 (10.34%) 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