Clinical trial results:
A Phase II Study of Radium-223 in Combination with Enzalutamide in Progressive Metastatic Castrate-Resistant Prostate Cancer

Summary

EudraCT number	2013-004850-97
Trial protocol	IE
Global end of trial date	23 November 2021

Results information

Result version number	v1 (current)
This version publication date	08 January 2023
First version publication date	08 January 2023

Trial information

Trial identification

Sponsor protocol code	13-21

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02225704
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cancer Trials Ireland
Sponsor organisation address	RCSI House, 121 St. Stephen’s Green, Dublin 2, Ireland, D02 H903
Public contact	Head of Clinical Operations, Cancer Trials Ireland, +353 16677211, regulatory@cancertrials.ie
Scientific contact	Head of Clinical Operations, Cancer Trials Ireland, +353 16677211, regulatory@cancertrials.ie

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	04 October 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 November 2021
Global end of trial reached?	Yes
Global end of trial date	23 November 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Objective: To determine the safety and tolerability of Radium-223 when administered in combination with enzalutamide in progressive metastatic castrate-resistant prostate cancer.

Protection of trial subjects:

The study was conducted in accordance with the EU Directive 2001/20/EC and International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). Site monitoring was performed from the time of initiation until study close-out and complied with EU directive 2001/20/EC and ICH GCP (CPMP/ICH/135/95) regulations.

Background therapy:

All patients had concurrent use of an agent for medical castration (e.g. Gonadotropin releasing hormone (GnRH) analogue).

Evidence for comparator:

N/A

Actual start date of recruitment	04 August 2015
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	Ireland: 45
Worldwide total number of subjects	45
EEA total number of subjects	45

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)	14
From 65 to 84 years	31
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study recruited a total of 47 patients. The first patient was enrolled in August 2015 and the last patient was recruited in July 2017.

Pre-assignment

Screening details:

Patients recruited to the study will have received a diagnosis for progressive metastatic castrate-resistant prostate cancer and must fulfil all inclusion criteria and none of the exclusion criteria outlined in protocol.

Pre-assignment period milestones

Number of subjects started	45
Number of subjects completed	45

Period 1

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

Blinding implementation details:

This study was a single arm non blinded study

Arms

Arm title	Single Arm

Arm description:

Single arm study of the combination of Radium-223 dichloride in combination with enzalutamide in progressive metastatic castrate-resistant prostate cancer.

Arm type	Experimental
Investigational medicinal product name	Radium -223 dichloride
Investigational medicinal product code	BAY 88-8223,
Other name	Xofigo
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

55kBq/kg slow bolus IV injection on Day 1 of every four week cycle, for a maximum of 6 cycles

Investigational medicinal product name	Enzalutamide
Investigational medicinal product code	
Other name	Xtandi
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

(160mg po daily; (4 x 40 mg capsules)) until disease progression, unacceptable toxicity, consent withdrawal or withdrawal for any other reason, or study close

Number of subjects in period 1	Single Arm
Started	45
Completed	10
Not completed	35
Died on-study (all in follow-up)	22
Consent withdrawn by subject	2
Study close-out	11

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	45	45	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	14	14	
From 65-84 years	31	31	
85 years and over	0	0	
Age continuous Units: years			
median	68.0		
full range (min-max)	51 to 79	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	45	45	
Ethnic Origin Units: Subjects			
Caucasion	45	45	

Subject analysis sets

Subject analysis set title	Overall Trial
Subject analysis set type	Full analysis

Subject analysis set description:

This subject analysis set is being created as a workaround to allow reporting of a statistical analysis on a single arm study.

Reporting group values	Overall Trial		
Number of subjects	45		
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)	14		
From 65-84 years	31		
85 years and over			
Age continuous			
Units: years			
median	68		
full range (min-max)	51 to 79		
Gender categorical			
Units: Subjects			
Female			
Male			
Ethnic Origin			
Units: Subjects			
Caucasion			

End points

End points reporting groups

Reporting group title	Single Arm

Reporting group description:

Single arm study of the combination of Radium-223 dichloride in combination with enzalutamide in progressive metastatic castrate-resistant prostate cancer.

Subject analysis set title	Overall Trial
Subject analysis set type	Full analysis

Subject analysis set description:

This subject analysis set is being created as a workaround to allow reporting of a statistical analysis on a single arm study.

Primary: The incidence of grade 3 or higher adverse events during the period of combination therapy will be recorded and graded according to the NCI - CTCAE criteria, version 4.

End point title	The incidence of grade 3 or higher adverse events during the period of combination therapy will be recorded and graded according to the NCI - CTCAE criteria, version 4.

End point description:

The primary endpoint is the grade 3/4 toxicity rate for the combination therapy, defined as the incidence of patients experiencing an adverse event of grade 3 toxicity or higher during the period of combination therapy.

End point type	Primary

End point timeframe:

From date of registration to the date of clinical /radiological disease progression or death, whichever is reported first.

End point values	Single Arm	Overall Trial		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	45	45		
Units: Adverse Events	45	45		

Statistical analyses

Statistical analysis title	Incidence rate of G3+ Combination Therapy AEs

Statistical analysis description:

The grade 3/4 toxicity rate presented as the percentage of patients in the safety population who experienced a grade 3 or higher toxicity during combination therapy, together with the accompanying two-sided 90% and 95% confidence intervals, calculated using the normal approximation.

Comparison groups	Single Arm v Overall Trial
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other[1]
Method	Incidence rate and confidence interval
Parameter estimate	Incidence rate
Point estimate	31.1

Confidence interval	
level	90 %
sides	2-sided
lower limit	19.8
upper limit	42.5

Notes:

[1] - Incidence rate and confidence interval

Secondary: Time to clinical/radiological progression

End point title	Time to clinical/radiological progression

End point description:

Time to clinical/radiological progression (as measured according to PCWG2 and RECIST 1.1 criteria). Clinical progression is defined as evidence of progression or recurrence on imaging, clinical examination, development of cancer related symptoms or treatment withdrawal for reasons of clinical progression

End point type	Secondary

End point timeframe:

From start of treatment to Clinical/Radiological Progression

End point values	Single Arm	Overall Trial		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	45	45		
Units: Months	45	45		

Statistical analyses

Statistical analysis title	Time to Clinical/Radiological Progression

Statistical analysis description:

For the ITT set of 45 patients, 24 patients (54.5%) progressed and 20 patients (45.5%) were censored at the date when last known to be progression-free, or the date of start of new anti-cancer treatment (including restart of enzalutamide) if earlier. One patient did not have any post-screening scans.

Comparison groups	Single Arm v Overall Trial
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other[2]
Parameter estimate	Median
Point estimate	28
Confidence interval	
level	95 %
sides	2-sided
lower limit	22.5
upper limit	61.2

Notes:

[2] - the Kaplan-Meier (1958) analysis for clinical/radiological PFS

Secondary: Time to PSA progression

End point title	Time to PSA progression

End point description:

The objective time to PSA (prostate specific antigen) progression of patients treated with Radium-223 in combination with enzalutamide in progressive metastatic castrate-resistant prostate cancer. Progression will be assessed in accordance with recommendations by the Prostate Cancer Working Group (PCWG2) criteria.

End point type	Secondary

End point timeframe:

From registration to PSA progression

End point values	Single Arm	Overall Trial		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	45	45		
Units: months	45	45		

Attachments (see zip file)	time to PSA Progression/Time to PSA Progression.png

Statistical analyses

Statistical analysis title	Time to PSA Progression

Statistical analysis description:

For the ITT set of 45 patients, 36 patients (80%) progressed, and 9 patients (20%) were censored at the date when last known to be progression-free, or the date of start of new anti-cancer treatment (including restart of enzalutamide) if earlier.
Median time to PSA progression was 18.1 months with 95% CI of [12.7 – 22.6] months.
The PFS rate at 12 months was estimated at 64.9% with 95% CI of [48.6 – 77.2].

Comparison groups	Single Arm v Overall Trial
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	Median difference (final values)
Point estimate	18.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.7
upper limit	22.6

Notes:

[3] - the Kaplan-Meier analysis

Secondary: PSA response (50% reduction from baseline)

End point title	PSA response (50% reduction from baseline)

End point description:

PSA Response is defined as 2 consecutive assessments at least 3 weeks apart with a reduction of at least 50% from baseline.

End point type	Secondary

End point timeframe:

PSA assessment every four weeks for a maximum of 6 cycles and every six weeks after until disease

progression, unacceptable toxicity, consent withdrawal or withdrawal for any other reason, or study close

End point values	Single Arm	Overall Trial		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	45	45		
Units: patients	45	45		

Statistical analyses

Statistical analysis title	PSA Response

Statistical analysis description:

PSA Response, defined as 2 consecutive assessments at least 3 weeks apart with a reduction of at least 50% from baseline for the ITT set. A total of 43 patients (95.6%) responded, with 95% CI [89.5% - 100%].

Comparison groups	Single Arm v Overall Trial
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other[4]
Parameter estimate	Median difference (final values)
Point estimate	43
Confidence interval	
level	95 %
sides	2-sided
lower limit	40
upper limit	45

Notes:

[4] - PSA response (50% reduction from baseline) presented as the percentage of patients with response, together with the accompanying two-sided 95% confidence interval, calculated using the normal approximation.

Secondary: Change in alkaline phosphatase

End point title	Change in alkaline phosphatase

End point description:

End point type	Secondary

End point timeframe:

Alkaline phosphatase assessment every four weeks for a maximum of 6 cycles and every six weeks after until disease progression, unacceptable toxicity, consent withdrawal or withdrawal for any other reason, or study close.

End point values	Single Arm	Overall Trial		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	45	45		
Units: IU/L	45	45		

Statistical analyses

Statistical analysis title	Change in alkaline phosphatase

Statistical analysis description:

The median baseline level was 99.0 IU/L (range of 39 – 964), which reduced to 66.5 IU/L (range of 30 – 107) after 6 cycles of study treatment. The median level at the end of study treatment was 90.5 IU/L (range of 34 – 534).

Comparison groups	Single Arm v Overall Trial
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other[5]
Parameter estimate	Median difference (final values)
Point estimate	66.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	30
upper limit	107

Notes:

[5] - Descriptive statistics presented for change in alkaline phosphatase from baseline

Secondary: Time to first skeletal-related event

End point title	Time to first skeletal-related event

End point description:

Skeletal-related events are defined as the first event of:
-the first use of external-beam radiation therapy to relieve skeletal symptoms,
-new pathologic vertebral or non-vertebral bone fractures,
-spinal cord compression, or
-tumor-related orthopedic surgical intervention
For the ITT set of 45 patients, 8 patients (17.8%) experienced an SRE and the remaining 37 patients (82.2%) were censored at the end of the 2 years follow up period. Because of the small number of events, the median time to first SRE and 95% CI were not estimable.

End point type	Secondary

End point timeframe:

The period for the reporting of all serious and non-serious skeletal related events was from date of consent to until the end of the 2 years follow-up period or until study close.

End point values	Single Arm	Overall Trial		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	45	45		
Units: months	45	45		

Statistical analyses

No statistical analyses for this end point

Secondary: Pain assessment (Brief Pain Inventory-Short Form)

End point title	Pain assessment (Brief Pain Inventory-Short Form)

End point description:

The Brief Pain Inventory-Short Form should be completed prior to any other study related procedures. Individual questions were scored on a scale of 0 – 10, where 0 represented no pain and 10 represented pain as bad as could be imagined.

End point type	Secondary

End point timeframe:

Pain assessment (Brief Pain Inventory-Short Form) every four weeks for a maximum of 6 cycles and every six weeks after until disease progression, unacceptable toxicity, consent withdrawal or withdrawal for any other reason, or study close.

End point values	Single Arm	Overall Trial		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	45	45		
Units: score	45	45		

Statistical analyses

Statistical analysis title	Pain assessment

Statistical analysis description:

Descriptive statistics will be presented for change in pain from baseline as assessed by the Brief Pain Inventory-Short Form. Pain severity score, calculated as the mean of the 4 individual pain question scores, (only calculated where >50%, or at least 3, of the individual scores are non-missing). The median severity score at baseline was 1.8 (range of 0 – 8), which was largely unchanged at median 1.9 (range of 0 – 6) after 6 cycles of study treatment.

Comparison groups	Single Arm v Overall Trial
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other[6]
Parameter estimate	Median difference (final values)
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	8

Notes:
[6] - Descriptive statistics

Secondary: Overall survival

End point title	Overall survival

End point description:

End point type	Secondary

End point timeframe:

From the date of registration to the date of death from any cause. Patients lost to follow up or those with no death recorded on the day the database is finalised will be censored on the date last known to be alive.

End point values	Single Arm	Overall Trial		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	45	45		
Units: months	45	45		

Attachments (see zip file)	Overall survival.png

Statistical analyses

Statistical analysis title	Overall Survival

Statistical analysis description:

For the ITT set of 45 patients, 22 patients (48.9%) died on study (20 from disease progression and 2 from adverse events unrelated to study treatment) and 23 patients (51.1%) were censored at the date when last known to be alive.
Median time to death was 51.1 months. Less than 50% of the patients had died and the 95% CI was not fully estimable, the lower bound was 35.3 months.

Comparison groups	Single Arm v Overall Trial
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other[7]
Parameter estimate	Median difference (final values)
Point estimate	51.1
Confidence interval	
level	95 %
sides	1-sided
lower limit	35.3

Notes:
[7] - the Kaplan-Meier analysis

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the date of patient's informed consent and up to 30 days after the end of study treatment.

Adverse event reporting additional description:

The intensity of the adverse events recorded as per CTCAE v4.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Overall Trial

Reporting group description:

Single arm study of the combination of Radium-223 dichloride and enzalutamide for a maximum of 6 cycles and enzalutamide alone after until disease progression, unacceptable toxicity, consent withdrawal or withdrawal for any other reason, or study close, in progressive metastatic castrate-resistant prostate cancer.

Serious adverse events	Overall Trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 45 (44.44%)		
number of deaths (all causes)	22		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adrenal gland cancer metastatic			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Carcinoid tumour of the appendix			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung adenocarcinoma			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma of the oral cavity			

subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Renal cell carcinoma				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Asthenia				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	2 / 45 (4.44%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Cough				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary hypertension				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Confusional state				

subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute myocardial infarction			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Parkinsonism	Additional description: Investigaton of Parkinson's symptoms		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Lymphopenia			

subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enterocutaneous fistula			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Pathological fracture			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Gingivitis			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Overall Trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 45 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Rectal neoplasm			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Metastases to spinal cord			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	12 / 45 (26.67%)		
occurrences (all)	45		
Hot flush			
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	7		
Haemorrhage			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Hypotension			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	3		
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Skin neoplasm excision			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	5		
Skin graft			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Transurethral prostatectomy			

subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
General disorders and administration site conditions			
Discomfort			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Suprapubic pain	Additional description: Suprapubic tenderness		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Influenza like illness			
subjects affected / exposed	6 / 45 (13.33%)		
occurrences (all)	7		
Chest pain			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	5		
Fatigue			
subjects affected / exposed	30 / 45 (66.67%)		
occurrences (all)	55		
Oedema			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	3		
Application site erythema			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	6 / 45 (13.33%)		
occurrences (all)	6		
Asthenia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Swelling	Additional description: Swelling in groin		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Malaise			

subjects affected / exposed	2 / 45 (4.44%)			
occurrences (all)	2			
Injection site pain				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Peripheral swelling				
subjects affected / exposed	2 / 45 (4.44%)			
occurrences (all)	2			
Feeling hot				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Infusion site extravasation				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Chest discomfort				
subjects affected / exposed	2 / 45 (4.44%)			
occurrences (all)	2			
Injection site reaction				
subjects affected / exposed	2 / 45 (4.44%)			
occurrences (all)	2			
Pyrexia				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Swelling face				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Chills				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Localised oedema				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Injection site haemorrhage				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Injection site nodule				

subjects affected / exposed occurrences (all) Non-cardiac chest pain subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1 1 / 45 (2.22%) 1 1 / 45 (2.22%) 1		
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all) Hypersensitivity subjects affected / exposed occurrences (all)	 1 / 45 (2.22%) 1 1 / 45 (2.22%) 1		
Reproductive system and breast disorders Prostate tenderness subjects affected / exposed occurrences (all) Gynaecomastia subjects affected / exposed occurrences (all) Pruritus genital subjects affected / exposed occurrences (all) Pelvic pain subjects affected / exposed occurrences (all) Testicular pain subjects affected / exposed occurrences (all) Balanoposthitis subjects affected / exposed occurrences (all)	 1 / 45 (2.22%) 1 7 / 45 (15.56%) 7 1 / 45 (2.22%) 1 1 / 45 (2.22%) 1 1 / 45 (2.22%) 1 1 / 45 (2.22%) 2		
Respiratory, thoracic and mediastinal disorders			

Cough				
subjects affected / exposed	2 / 45 (4.44%)			
occurrences (all)	5			
Nasal discomfort				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Wheezing				
subjects affected / exposed	3 / 45 (6.67%)			
occurrences (all)	3			
Pulmonary infarction				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Dyspnoea				
subjects affected / exposed	3 / 45 (6.67%)			
occurrences (all)	4			
Oropharyngeal pain				
subjects affected / exposed	2 / 45 (4.44%)			
occurrences (all)	2			
Dyspnoea exertional				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Dysphonia				
subjects affected / exposed	2 / 45 (4.44%)			
occurrences (all)	2			
Productive cough				
subjects affected / exposed	3 / 45 (6.67%)			
occurrences (all)	3			
Pulmonary mass				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Epistaxis				
subjects affected / exposed	2 / 45 (4.44%)			
occurrences (all)	2			
Rhinorrhoea				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			

Pulmonary embolism			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Pulmonary hypertension			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Psychiatric disorders			
Disorientation			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Anxiety			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Depressed mood			
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	6		
Insomnia			
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	6		
Confusional state			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Tearfulness			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Nightmare			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Investigations			
Neutrophil count decreased			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Weight increased			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Weight decreased			

subjects affected / exposed	12 / 45 (26.67%)			
occurrences (all)	21			
Blood magnesium decreased				
subjects affected / exposed	3 / 45 (6.67%)			
occurrences (all)	4			
White blood cell count decreased				
subjects affected / exposed	5 / 45 (11.11%)			
occurrences (all)	15			
Lymphocyte count decreased				
subjects affected / exposed	5 / 45 (11.11%)			
occurrences (all)	10			
Intraocular pressure increased				
subjects affected / exposed	2 / 45 (4.44%)			
occurrences (all)	2			
Electrocardiogram QT prolonged				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Blood urine present				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Alanine aminotransferase increased				
subjects affected / exposed	2 / 45 (4.44%)			
occurrences (all)	2			
Aspartate aminotransferase increased				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Gamma-glutamyltransferase increased				
subjects affected / exposed	2 / 45 (4.44%)			
occurrences (all)	2			
Blood alkaline phosphatase increased				
subjects affected / exposed	3 / 45 (6.67%)			
occurrences (all)	3			
Blood glucose increased				

subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Blood cholesterol increased			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Blood folate decreased			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Blood phosphorus decreased			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	2		
Blood potassium decreased			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	2		
Blood creatinine increased			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	7		
C-reactive protein increased			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Blood iron decreased			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Blood urea increased			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	3		
Blood calcium increased			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Pulse absent	Additional description: Pedal pulse absent right foot		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Blood potassium increased			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Injury, poisoning and procedural			

complications				
Fractured sacrum				
subjects affected / exposed	2 / 45 (4.44%)			
occurrences (all)	2			
Acetabulum fracture				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Thyroid gland injury				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Procedural pain				
subjects affected / exposed	3 / 45 (6.67%)			
occurrences (all)	3			
Scratch				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Stoma site haemorrhage				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Rib fracture				
subjects affected / exposed	5 / 45 (11.11%)			
occurrences (all)	7			
Lumbar vertebral fracture				
subjects affected / exposed	3 / 45 (6.67%)			
occurrences (all)	5			
Fall				
subjects affected / exposed	7 / 45 (15.56%)			
occurrences (all)	8			
Ligament sprain				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Tibia fracture				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Joint injury				

subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Ankle fracture				
subjects affected / exposed	2 / 45 (4.44%)			
occurrences (all)	2			
Infusion related reaction				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Forearm fracture				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Femur fracture				
subjects affected / exposed	2 / 45 (4.44%)			
occurrences (all)	2			
Radiation mucositis				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Ligament rupture				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Thoracic vertebral fracture				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Skin wound				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Hyphaema				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Sunburn				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Skin laceration				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Animal bite				

subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Toxicity to various agents			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Cardiac failure			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Sinus bradycardia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Conduction disorder			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Bradycardia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Atrial fibrillation			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	2		
Bundle branch block right			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 45 (13.33%)		
occurrences (all)	7		
Burning sensation			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Headache			

subjects affected / exposed	12 / 45 (26.67%)		
occurrences (all)	17		
Memory impairment	Additional description: Short memory disturbance		
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	5		
Lumbosacral radiculopathy			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Ageusia			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Dyskinesia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Migraine			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	3		
Restless legs syndrome			
subjects affected / exposed	8 / 45 (17.78%)		
occurrences (all)	8		
Amnesia			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Hypoaesthesia			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	4		
Disturbance in attention			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Neuropathy peripheral			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Presyncope			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	3		
Sciatica			

subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1		
Syncope subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1		
Paraesthesia subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 4		
Dysgeusia subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1		
Parkinson's disease subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1		
Dysaesthesia subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	10 / 45 (22.22%) 16		
Neutropenia subjects affected / exposed occurrences (all)	9 / 45 (20.00%) 21		
Thrombocytopenia subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1		
Ear and labyrinth disorders Ear congestion subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1		
Vertigo subjects affected / exposed occurrences (all)	2 / 45 (4.44%) 2		
Tinnitus			

subjects affected / exposed occurrences (all)	4 / 45 (8.89%) 4		
Excessive cerumen production subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1		
Ear pain subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 2		
Deafness subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1		
Eye disorders			
Lacrimation increased subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1		
Eye pain subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1		
Ocular hyperaemia subjects affected / exposed occurrences (all)	2 / 45 (4.44%) 2		
Vitreous floaters subjects affected / exposed occurrences (all)	2 / 45 (4.44%) 3		
Gastrointestinal disorders			
Nausea subjects affected / exposed occurrences (all)	26 / 45 (57.78%) 53		
Anorectal discomfort subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1		
Constipation subjects affected / exposed occurrences (all)	11 / 45 (24.44%) 11		
Abdominal pain			

subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Diarrhoea			
subjects affected / exposed	24 / 45 (53.33%)		
occurrences (all)	32		
Dyspepsia	Additional description: Indigestion		
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	4		
Loose tooth			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Gastrooesophageal reflux disease			
subjects affected / exposed	6 / 45 (13.33%)		
occurrences (all)	9		
Vomiting			
subjects affected / exposed	8 / 45 (17.78%)		
occurrences (all)	13		
Abdominal pain upper			
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	7		
Toothache			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Rectal haemorrhage			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Tongue blistering			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Abdominal discomfort			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Mouth ulceration			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Oral pain			

subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Abdominal pain lower			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	4		
Frequent bowel movements			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Gingival pain			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Noninfective gingivitis			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Tongue discolouration			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Tongue haemorrhage			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Barrett's oesophagus			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Anal haemorrhage			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Gastrointestinal motility disorder			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	6		
Rash			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	4		

Pruritus				
subjects affected / exposed	2 / 45 (4.44%)			
occurrences (all)	2			
Skin lesion				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Rash maculo-papular				
subjects affected / exposed	2 / 45 (4.44%)			
occurrences (all)	3			
Dermatitis exfoliative generalised				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Urticaria				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Petechiae				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Hidradenitis				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Skin discolouration				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Rash papular				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Ingrowing nail				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Nail disorder				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Alopecia				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			

Renal and urinary disorders			
Pollakiuria	Additional description: Increased urinary frequency		
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Bladder spasm			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Dysuria			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Urinary retention			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Nocturia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Haematuria			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Bladder hypertrophy			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Micturition urgency			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Hydroureter			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Hydronephrosis			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Adrenal mass			

subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	18 / 45 (40.00%)		
occurrences (all)	30		
Pain in extremity			
subjects affected / exposed	11 / 45 (24.44%)		
occurrences (all)	18		
Bone pain			
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	12		
Myalgia			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Arthralgia			
subjects affected / exposed	22 / 45 (48.89%)		
occurrences (all)	31		
Sacral pain			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Pain in jaw			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	4		
Musculoskeletal chest pain			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	5		
Arthritis			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	2		
Muscular weakness			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Rheumatoid arthritis			

subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Osteoporotic fracture			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Osteonecrosis of jaw			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Pubic pain			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Plantar fasciitis			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Musculoskeletal stiffness			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	3		
Neck pain			
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	7		
Groin pain			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	2		
Pathological fracture			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	5		
Furuncle			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		

Sinusitis				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Localised infection				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Eye infection				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Nasopharyngitis				
subjects affected / exposed	8 / 45 (17.78%)			
occurrences (all)	13			
Viral upper respiratory tract infection				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Cellulitis				
subjects affected / exposed	2 / 45 (4.44%)			
occurrences (all)	2			
Stoma site cellulitis				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Wound infection				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Respiratory tract infection				
subjects affected / exposed	3 / 45 (6.67%)			
occurrences (all)	3			
Gingivitis				
subjects affected / exposed	3 / 45 (6.67%)			
occurrences (all)	9			
Osteomyelitis				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	2			
Penile infection				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			

Gastroenteritis			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Ear infection			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Lower respiratory tract infection			
subjects affected / exposed	9 / 45 (20.00%)		
occurrences (all)	11		
Conjunctivitis			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Otitis media			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Candida infection			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Tinea pedis			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Skin infection			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	3		
Ludwig angina			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	14 / 45 (31.11%)		
occurrences (all)	18		
Hypoalbuminaemia			

subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Hypercalcaemia				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	2			
Hypercholesterolaemia				
subjects affected / exposed	2 / 45 (4.44%)			
occurrences (all)	2			
Hyperglycaemia				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Hypophosphataemia				
subjects affected / exposed	2 / 45 (4.44%)			
occurrences (all)	3			
Hypertriglyceridaemia				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Vitamin B12 deficiency				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Appetite disorder				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Hyponatraemia				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	2			
Hypokalaemia				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Hyperkalaemia				
subjects affected / exposed	2 / 45 (4.44%)			
occurrences (all)	3			
Iron deficiency				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Dehydration				

subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 October 2015	Incorporation of the requirement to implement National Institute of Standards and Technology (NIST) update changes in regards to Radium 223 dose, Reference Safety information updated for both study drugs. Translational section revised to increase in blood volume collected. Inclusion and exclusion criteria amended due to reference safety information updates and CHAARTED trial. Included administrative changes and an update to the statistical considerations and Safety
17 May 2018	Administrative changes to include update to sponsor's name, staff changes and removal of a study site. Also included a change to Radium dose as per NIST update and addition of 2 study objectives to correspond to 2 listed study endpoints. Update to reference safety data for Xtandi and Radium-223. Update to estimated study completion date. Changes of wording to further clarify protocol details. Change of AE reporting timeline from 28 to 30 days after study treatment and wording changes to clarify reporting.
22 November 2019	Changes in wording to define clinical progression - wherever radiological progression was mentioned, this is replaced with clinical/radiological progression. Clarification added that if patients recommence Enzalutamide in the follow up period, this will be considered as a new treatment.
25 January 2021	Amendment to the protocol to facilitate closure of the trial. Enzalutamide is considered standard of care treatment in this setting and is available to patients outside of this clinical trial. The protocol is amended so that all patients on enzalutamide treatment will discontinue study treatment and will complete a post-treatment withdrawal visit 30 to 42 days after the last dose and will be taken off study. These patients may continue with enzalutamide treatment outside of the study as per standard of care. Patients in follow up for survival at study close will cease all follow up visits/calls.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34512801