



Clinical trial results:

Neo-adjuvant Androgen Deprivation Therapy, Pelvic Radiotherapy and Radium-223 for new presentation T1-4 N0/1 M1B adenocarcinoma of prostate (ADRRAD Trial)

Summary

EudraCT number	2014-000273-39
Trial protocol	GB
Global end of trial date	04 August 2022

Results information

Result version number	v1 (current)
This version publication date	19 August 2023
First version publication date	19 August 2023

Trial information

Trial identification

Sponsor protocol code	14095JOS-SS
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Belfast Health and Social Care Trust
Sponsor organisation address	East Podium, C floor, Belfast, United Kingdom, BT9 7AB
Public contact	Prof Joe O'Sullivan, Belfast Health and Social Care Trust, 0044 2895048349, rebecca.gallagher@belfasttrust.hscni.net
Scientific contact	Prof Joe O'Sullivan, Belfast Health and Social Care Trust, 0044 2895048349, rebecca.gallagher@belfasttrust.hscni.net

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	07 September 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 September 2020
Global end of trial reached?	Yes
Global end of trial date	04 August 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the safety, toxicity and feasibility of the combination of ADT + Radium-223 + IMRT in men with castration sensitive, M1b metastatic prostate cancer with a view to larger future randomised trials.

Protection of trial subjects:

The trial was comprehensively discussed with all participants in advance of informed consent. All participants were screened for eligibility prior to registration on the trial. Adverse events were assessed at baseline, weekly during Radiation and Radium-223 treatment and six weeks post treatment. Adverse events were followed up until resolution. Trial safety was part of the remit of the Trial Management Group meeting which were held monthly during treatment and 3-monthly during follow up. An Independent Data Monitoring Committee was appointed to study safety and efficacy data during the study. Safety and efficacy data was reviewed on a periodic basis, approximately every 6 months from enrolment of the first patient until the end of the study. Following all Independent Data Monitoring Committee meetings, recommendations were provided to the Trial Management Group and Trial Sponsor.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 January 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 30
Worldwide total number of subjects	30
EEA total number of subjects	0

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)	19
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Thirty patients were recruited to the study. Eligible patients had been diagnosed with histologically confirmed de-novo bone metastatic hormone sensitive prostate cancer and had an ECOG performance status of 0-1. All participants had at least three bone metastases demonstrated on bone scan and no visceral metastases on CT/thorax/abdo/pelvis

Pre-assignment

Screening details:

Thirty three patients were consented to the study, thirty one, of which, were found to be eligible and were registered on study. Thirty patients received study treatment and were deemed evaluable

Pre-assignment period milestones

Number of subjects started	31 ^[1]
Number of subjects completed	30

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Disease progression: 1
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Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Thirty one patients were registered on study. However, one patient was withdrawn from study prior to treatment initiation due to disease progression.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Treatment
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Radium-223
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

The dose regimen for Xofigo is an activity of 55kBq per Kg body weight, given at 4 week intervals for six injections

Investigational medicinal product name	Zoladex 3.6mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Implant in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

One 3.6mg depot of Zoladex injected subcutaneously into the anterior abdominal wall every 28 days.

Investigational medicinal product name	Zoladex LA 10.8mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Implant in pre-filled syringe

Routes of administration	Subcutaneous use
Dosage and administration details:	
One depot of Zoladex LA injected subcutaneously into the anterior abdominal wall every 12 weeks	
Investigational medicinal product name	Decapeptyl SR 3mg
Investigational medicinal product code	
Other name	Triptorelin acetate
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Intramuscular use
Dosage and administration details:	
One intramuscular injection administered every 4 weeks	
Investigational medicinal product name	Decapeptyl SR 11.25 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Intramuscular use
Dosage and administration details:	
One intramuscular injection administered every 3 months	
Investigational medicinal product name	Prostap SR DCS 11.25 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for suspension for injection in pre-filled syringe
Routes of administration	Subcutaneous use
Dosage and administration details:	
The usual recommended dose is 11.25mg presented as a three month depot injection and administered as a single subcutaneous injection at intervals of 3 months	
Investigational medicinal product name	PROSTAP SR DCS 3.75mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for prolonged-release suspension for injection in pre-filled syringe
Routes of administration	Subcutaneous use
Dosage and administration details:	
3.75 mg presented as a one month depot injection and administration as a single subcutaneous or intramuscular injection every month.	

Number of subjects in period 1	Treatment
Started	30
Completed	30

Baseline characteristics

Reporting groups

Reporting group title	Treatment
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Reporting group description: -

Reporting group values	Treatment	Total	
Number of subjects	30	30	
Age categorical			
Units: Subjects			
Adults (18-64 years)	19	19	
From 65-84 years	11	11	
85 years and over	0	0	
Age continuous			
Units: years			
median	64		
full range (min-max)	45 to 82	-	
Gender categorical			
Units: Subjects			
Male	30	30	

End points

End points reporting groups

Reporting group title	Treatment
Reporting group description: -	

Primary: Gastrointestinal (GI) adverse events

End point title	Gastrointestinal (GI) adverse events ^[1]
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End point description:

Within the gastrointestinal domain, the most frequent adverse event observed was diarrhoea. Twenty five patients (83.3%) experienced diarrhoea, which was grade 1-2 in all patients. There were no grade 3, 4 or 5 gastrointestinal events observed during the conduct of the study.

End point type	Primary
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End point timeframe:

Adverse events were assessed from Informed Consent until 8 weeks post last radium-223 infusion.

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: In this Phase I/II trial, gastrointestinal adverse events are expressed as rates.

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: Number of patients				
GI Toxicity Grade 1	22			
GI Toxicity Grade 2	7			
GI Toxicity Grade 3	0			

Statistical analyses

No statistical analyses for this end point

Primary: Genito-urinary adverse events

End point title	Genito-urinary adverse events ^[2]
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End point description:

During the six weeks of treatment and 8-week follow up period, grade 1 to grade 3 adverse events were observed in the genito-urinary (GU) domain. Seventeen patients (56.7%) experienced dysuria, with one patient experiencing a grade 3. One additional patient experienced a grade 3 urinary tract infection (UTI) which responded to antibiotic therapy.

End point type	Primary
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End point timeframe:

Adverse events were assessed from informed consent until 8 weeks after final radium-223 infusion using common Terminology Criteria for Adverse event (CTCAE) v 4.03

Notes:

[2] - 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: In this Phase I/II trial, Genito-urinary adverse events are expressed as rates.

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: Number of patients				
Genito-urinary adverse events grade 1	18			
Genito-urinary adverse events grade 2	8			
Genito-urinary adverse events grade 3	1			

Statistical analyses

No statistical analyses for this end point

Primary: Quality of Life: bowel and urinary domains

End point title	Quality of Life: bowel and urinary domains ^[3]
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End point description:

Mean domain scores were calculated. There was a significant fall in bowel and urinary scores between screening and the start of cycle 3, that is, during the concurrent phase of treatment (mean bowel score at screening = 95.10, mean bowel score C3 = 81.0 P<0.001; mean urinary score at screening was 90.48 compared to the mean urinary score at cycle 3 which was 79.02 P = 0.003. These scores recover such that there is no significant difference between scores at screening and scores at the end of trial in either domain.

End point type	Primary
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End point timeframe:

Patients completed EPIC scores at screening, q4 weekly during radium-223 treatment, at 8 weeks post final radium-223 treatment and six months later at the end of study.

Notes:

[3] - 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: Mean domain scores were calculated with P values reported in the description.

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: Change in mean EPIC Scores				
number (not applicable)				
Mean bowel scores at screening	95.10			
Mean bowel scores at cycle 3	81.0			
Mean urinary scores at screening	90.48			
Mean urinary scores at cycle 3	79.02			

Statistical analyses

No statistical analyses for this end point

Secondary: Tumour response

End point title	Tumour response
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End point description:

Scans were compared pairwise within each patient, screening to post 6 cycle radium 223 and post cycle

6 to end of study. Scans were reported in categorial fashion based on overall disease behaviour showing: Tumour Burden (TB) increase, TB stable, TB reduction and TB resolution. Tumour burden increase was identified by a 25% increase in size of the lesion. The development of peri-lesional edema was also noted as a likely indicator of increasing tumour burden. TB reduction was indicated by a 50% decrease in the size of the lesion with replacement of the peripheral margin of the lesion by normal fatty marrow. Loss of peri-lesion edema was also noted as a likely indicator of tumour response. Stability fell between these definitions. TB resolution was indicated by complete resolutions of lesions.

End point type	Secondary
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End point timeframe:

Patients had a whole body MRI performed at screening, 8 weeks post final radium-223 infusion and again at 6 months post final radium-223 infusion.

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: Number of patients				
Tumour burden resolved at 6 months	6			
Tumour burden reduced at 6 months	16			
Tumour burden stable at 6 months	2			
Tumour burden increased at 6 months	4			
Tumour burden resolved at 12 months	7			
Tumour burden reduced at 12 months	9			
Tumour burden stable at 12 months	1			
Tumour burden increased at 12 months	11			

Statistical analyses

No statistical analyses for this end point

Secondary: Alkaline phosphatase (ALP) Response

End point title	Alkaline phosphatase (ALP) Response
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End point description:

ALP was measured as a marker of biochemical response and bone health. ALP was expressed as means per timepoint. Between screening and cycle 6 Radium-223 (6 months), ALP fell in 27 patients (90%). This trend reverses 6 months later, at end of study, where fifteen patients were shown to have a decrease in ALP at this timepoint compared to screening.

End point type	Secondary
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End point timeframe:

All patients had Alkaline Phosphatase (ALP) measured q4 weekly during treatment, at 8 weeks post final Radium-223 injection and again at end of study (6 months post final Radium-223 injection).

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: Number of patients				
Decrease in ALP at 6 months	27			
Decrease in ALP at 12 months	15			

Statistical analyses

No statistical analyses for this end point

Secondary: Symptomatic Skeletal Events

End point title	Symptomatic Skeletal Events
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End point description:

During the trial, no patient received bone health treatment, as was standard for metastatic hormone sensitive prostate cancer patients at this time. In terms of fractures, in total 8 patients (26.7%) experienced at least one malignant fracture, 3 (10%) patients experienced at least one fragility fracture and 1 patient (3.3%) experienced two traumatic fractures. Nine courses of palliative radiotherapy were delivered, eight for bone pain and one for spinal cord compression.

End point type	Secondary
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End point timeframe:

Patients were followed up for skeletal outcomes for 2 years following treatment.

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: Number of patients	6			

Statistical analyses

No statistical analyses for this end point

Secondary: Alkaline phosphatase response

End point title	Alkaline phosphatase response
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End point description:

Between screening and cycle 6 of radium-223, ALP fell in 27 patients (90%). This trend reverses 6 months later at the end of study, at this time point 15 patients (50%) have shown ALP increase relative to screening.

End point type	Secondary
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End point timeframe:

Alkaline phosphatase (ALP) was measured q4 weekly during treatment, at 8 weeks post final radium infusion and again at end of study, 6 months post final radium-223 infusion

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: Number of patients	27			

Statistical analyses

No statistical analyses for this end point

Secondary: Biochemical progression free survival

End point title	Biochemical progression free survival
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End point description:

Time to PSA progression was defined by PCWG2 criteria; 25% or greater increase and an absolute increase of 2ng/mL or more from the nadir. Survival times were calculated from the time of administration of first pretrial docetaxel for those patients who received it or trial registration for patients in whom docetaxel was contraindicated. This accounts for the mix of patients, 28 of whom were post docetaxel and 2 of whom were not. Median progression free survival was calculated by Kaplan-Meier methods. Median overall survival had not yet been reached.

End point type	Secondary
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End point timeframe:

Patients has PSA measured q4 weekly during treatment, at 8 weeks post final radium-223 infusion and again at end of study, 6 months post final radiun-223 infusion.

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: Months				
number (not applicable)	20.5			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events were reported from consent to 2 months post last Radium-223 injection.

Assessment type	Systematic
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Dictionary used

Dictionary name	CTCAE
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Dictionary version	4.03
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Reporting groups

Reporting group title	All patients
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Reporting group description: -

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 30 (13.33%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Chest pain-cardiac			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Renal and urinary disorders			
Cystitis non-infective			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Urinary Tract Infection			

subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 30 (100.00%)		
Vascular disorders			
HOT FLASHES			
subjects affected / exposed	6 / 30 (20.00%)		
occurrences (all)	6		
POSTURAL HYPOTENSION			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
THROMBOEMBOLIC EVENT (PULMONARY EMBOLUS)			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	18 / 30 (60.00%)		
occurrences (all)	18		
Head cold			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Psychiatric disorders			

DEPRESSION			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
INSOMNIA			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
LOW MOOD			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Investigations			
GGT INCREASED			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	2		
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	22 / 30 (73.33%)		
occurrences (all)	43		
PLATELET COUNT DECREASED			
subjects affected / exposed	8 / 30 (26.67%)		
occurrences (all)	12		
WEIGHT LOSS			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
WHITE BLOOD CELL DECREASED			
subjects affected / exposed	27 / 30 (90.00%)		
occurrences (all)	68		
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
UREA INCREASED			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
ANKLE FRACTURE			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
RIGHT ELBOW TRAUMATIC			

FRACTURE			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Cardiac disorders			
Chest pain-cardiac			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
LETHARGY			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
PERIPHERAL NEUROPATHY			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
PRESYNCOPE			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
SYNCOPE			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	14 / 30 (46.67%)		
occurrences (all)	18		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	8 / 30 (26.67%)		
occurrences (all)	11		
Abdominal cramps			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	4		
Abdominal discomfort			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		

Bowel Frequency			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	4		
Constipation			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	4		
Diarrhoea			
subjects affected / exposed	22 / 30 (73.33%)		
occurrences (all)	41		
Faecal urgency			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Flatulence			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
HAEMORRHOIDAL HAEMORRHAGE			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
LEFT SIDED ABDOMINAL DISCOMFORT			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
LOOSE STOOL			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	5		
RECTAL HAEMORRHAGE			
subjects affected / exposed	7 / 30 (23.33%)		
occurrences (all)	7		
VOMITING			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
ABDOMINAL PAIN			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	4		
BOWEL URGENCY			

subjects affected / exposed occurrences (all) RECTAL URGENCY subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1 1 / 30 (3.33%) 1		
Hepatobiliary disorders Jaundice subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1		
Skin and subcutaneous tissue disorders INSECT BITE subjects affected / exposed occurrences (all) PSOARIATIC FLARE subjects affected / exposed occurrences (all) SKIN REACTION subjects affected / exposed occurrences (all) SKIN RASH subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1 1 / 30 (3.33%) 1 2 / 30 (6.67%) 3 1 / 30 (3.33%) 1		
Renal and urinary disorders ACUTE KIDNEY INJURY subjects affected / exposed occurrences (all) CYSTITIS NON-INFECTIVE subjects affected / exposed occurrences (all) DYSURIA subjects affected / exposed occurrences (all) HAEMATURIA subjects affected / exposed occurrences (all) NOCTURIA	1 / 30 (3.33%) 1 4 / 30 (13.33%) 5 15 / 30 (50.00%) 18 1 / 30 (3.33%) 1		

subjects affected / exposed	18 / 30 (60.00%)		
occurrences (all)	26		
URINARY FREQUENCY			
subjects affected / exposed	9 / 30 (30.00%)		
occurrences (all)	10		
URINARY HESITANCY			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences (all)	5		
URINARY INCONTINENCE			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
URINARY URGENCY			
subjects affected / exposed	6 / 30 (20.00%)		
occurrences (all)	7		
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	9 / 30 (30.00%)		
occurrences (all)	10		
ARTHRITIS RIGHT HAND			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
BACK PAIN			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	5		
BONE PAIN LUMBAR SPINE			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
ENDPLATE FRACTURE			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
IMPENDING SPINAL CORD COMPRESSION			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
INSUFFICIENCY FRACTURE SACRAL ALA			

subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
KNEE PAIN			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
LEFT ANTERIOR CHEST DISCOMFORT			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
LEFT ELBOW PAIN			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
LEFT HUMERAL PAIN			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
LEFT SHOULDER PAIN			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	2		
LOWER BACK PAIN			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
MUSCULOSKELETAL PAIN			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
OSTEOPATHIC FRACTURE T7			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
PAIN RIGHT GROIN			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	2		
PATHOLOGICAL FRACTURE AT T4 AND L4			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
PATHOLOGICAL FRACTURE OF 5TH RIB			

subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
PATHOLOGICAL FRACTURE OF L1, L2 AND L5			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
PATHOLOGICAL FRACTURE OF T10, L3 AND L4			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
PATHOLOGICAL FRACTURE OF T3			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
PATHOLOGICAL FRACTURE OF T4 AND L1			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
PATHOLOGICAL FRACTURE OF T8			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
PATHOLOGICAL VERTEBRAL FRACTURES			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
RIB INJURY			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
RIGHT HIP PAIN			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	2		
RIGHT PELVIC PAIN			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
THUMB PAIN			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
VERTEBRAL FRACTURE			

subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Infections and infestations			
BRONCHIAL INFECTION			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
CORYZAL INFECTION			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
GASTROINTESTINAL INFECTION			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Lung infection			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
ORAL HERPES ZOSTER			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
SHINGLES			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
SKIN INFECTION			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	2		
CHEST INFECTION			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Metabolism and nutrition disorders			

ANOREXIA			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	4		
HYPOPHOSPHATEMIA			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 October 2015	The protocol was amended to reflect the US National Institute of Standards and Technology update of the reference standard resulting in the numerical description of the patient dose being adjusted from 50 kBq/kg to 55 kBq/kg.
13 April 2016	This amendment included the following:-The protocol was updated to include exclusion criteria to ensure that any patients receiving chemotherapy prior to trial entry had a suitable delay, to ensure bone marrow recovery before receiving radionuclide in this study. This was in response to a UK change in standard of care where docetaxel treatment became standard of care for men with newly diagnosed hormone sensitive metastatic prostate cancer, where eligible. Also, the US National Institute of Standards and Technology updated the reference standard resulting in the numerical description of the patient dose being adjusted from 50 kBq/kg to 55 kBq/kg, the patient information sheet was updated to include this. In addition the RSI for the study was updated.
06 October 2016	The protocol was amended to update the requirements for extra blood to be taken for an exploratory end point.
15 March 2017	This substantial amendment included the following: The protocol was updated to change the PSA threshold from 5ng/mL to 20ng/mL to allow patients to progress into the radiation treatment phase of the study. In addition, overall survival was added as an exploratory end point. Furthermore, the recruitment end date and study end date was extended. This amendment also included updates to the Reference Safety Information for the study.
21 September 2018	The ADRRAD protocol also underwent a substantial protocol amendment in response to the issue of the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) recommendations (dated 13 July 2018) restricting the use of Xofigo®. The recommendations were issued following the early unblinding of the ERA-223 randomised controlled trial, combining radium-223 with abiraterone due to concerns about increase of fracture rate and deaths in the combination group. In response to this, the ADRRAD study was amended to include collection of data on bone health up to 24 months post radium-223 treatment initiation. In addition, the patient information sheet was updated to include information on the risk of Xofigo® when combined with abiraterone. Also, there was a update to the Reference Safety Information for one of the LHRH analogues used in the study. The study recruitment date was extended.
16 September 2019	There was an update to the reference Safety Information for Xofigo.

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/34187853>