Toxicity and Efficacy of Concurrent Androgen Deprivation Therapy, Pelvic Radiotherapy, and Radium-223 in Patients with *De Novo* Metastatic Hormone-Sensitive Prostate Cancer

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ABSTRACT

Purpose: Radium-223 is an alpha-emitting radionuclide associated with overall survival (OS) improvement in metastatic castration-resistant prostate cancer (mCRPC). External beam radiotherapy (EBRT) to prostate extends OS in men with metastatic hormone-sensitive prostate cancer (mHSPC) limited to less than 4 metastases. We hypothesized that combination radium-223 + pelvic EBRT could safely deliver maximal radiotherapy doses to primary and metastatic prostate cancer and may improve disease control.

Patients and Methods: Thirty patients with *de novo* bone metastatic mHSPC who had commenced androgen deprivation therapy (ADT) and docetaxel were recruited to this single-arm, open-label, prospective clinical trial: Neo-adjuvant Androgen Deprivation Therapy, Pelvic Radiotherapy and RADium-223 (ADRRAD; for new presentation T1–4 N0–1 M1B adenocarcinoma of prostate). Study treatments were: ADT, 6 cycles of radium-223 q28 days, conventionally fractionated prostate radiotherapy (74 Gy) and simultaneous integrated boost to pelvic lymph nodes (60 Gy).

Results: No grade 4/5 toxicity was observed. Three patients experienced grade 3 leukopenia, and 1 each experienced grade 3 neutropenia and thrombocytopenia; all were asymptomatic. One patient each experienced grade 3 dysuria and grade 3 urinary infection. No grade 3 gastrointestinal (GI) toxicity was observed. On treatment completion, there was a signal of efficacy; 24 (80%) patients had whole-body MRI evidence of tumor response or stability. Twenty-seven (90%) patients showed a reduction in alkaline phosphatase (ALP) compared with pretreatment levels. Median progression-free survival was 20.5 months.

Conclusions: This is the first trial of combination ADT, radium-223, and EBRT to pelvis, post docetaxel. The combination was safe, with an efficacy signal. Multicenter randomized controlled trials (RCT) are warranted.

Introduction

Prostate cancer is the second commonest cancer diagnosed in men globally; in 2018 an estimated 1,276,106 cases were diagnosed (1). In developed healthcare economies prostate cancer may present with metastases (metastatic hormone sensitive prostate cancer; mHSPC) in up to 19% of cases (2). This is a lethal disease, typically progressing from mHSPC to metastatic castration-resistant prostate cancer (mCRPC). For newly diagnosed patients commencing standard treatment with androgen deprivation therapy (ADT), recent data suggest they will remain sensitive to castration therapy for a median of 11 months before progression; median overall survival (OS) in this group was found to be 42 months (3). The most common site of metastases in prostate cancer is the skeleton and it is estimated 85%–100% of men who die of prostate cancer will have bone metastases (4). Bone metastases from prostate cancer are a significant source of disability and treatment cost; also bone disease and its complications are a frequent cause of death in patients with prostate cancer (5). Therefore, *de-novo* metastatic prostate cancer represents a common illness, which is a major cause of morbidity and mortality.

Historically the treatment of mHSPC consisted of castration until progression, typically with luteinizing hormone releasing hormone agonists (LHRHa; ref. 6). Castration remains essential, however recently a number of systemic therapies have been found to improve survival when commenced at the initiation of castration; these are docetaxel (7, 8), abiraterone acetate (9, 10) enzalutamide (11, 12), and apalutamide (13). Notably these compounds were initially found to have activity in later mCRPC before being tested in hormone sensitive disease (14–19).

In localized disease, radiotherapy can be curative (20–22). In mHSPC with low volume metastases (<4), external beam radiotherapy (EBRT) to the primary cancer has recently been found to improve OS(23). In mCRPC a range of bone-seeking radionuclides have been utilized effectively to palliate bone pain from metastases (24). More recently the alpha-particle emitting radionuclide radium-223 has been shown to extend survival in mCRPC. The ALSYMPCA trial was a phase III, double-blind randomized controlled trial (RCT) in which patients with symptomatic mCRPC received either 6 cycles of radium-223 (activity 55kBq/kg) or placebo. It demonstrated significant OS prolongation (HR = 0.7 $P < 0.001$) as well as delay to the development of first symptomatic skeletal event (SSE; ref. 25).

We designed a prospective clinical trial to test the combination of radium-223 with concurrent EBRT to prostate and pelvic lymph nodes

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Translational Relevance

Recent evidence has shown the survival prolonging advantage of both radionuclide therapy with radium-223 and of external beam radiotherapy to prostate in metastatic prostate cancer. A wave of ongoing trials are investigating other types of molecular radiotherapy, including the use of alternative radionuclides. With a range of survival prolonging treatments licensed in the past 5 years for metastatic prostate cancer, combinations of these treatments are increasingly being explored. We report the first trial to examine the combination of androgen deprivation therapy, upfront docetaxel, radium-223, and external beam radiotherapy to prostate and pelvis in metastatic hormone sensitive prostate cancer (mHSPC). The results demonstrate this treatment combination is well tolerated with encouraging efficacy results.

in men with mHSPC involving the skeleton, following neo-adjuvant ADT (minimum 6 months) and up to 6 cycles of upfront docetaxel (unless patient ineligible). This combination of therapies potentially allows delivery of radiation to all sites of disease (EBRT to primary and pelvic lymph nodes, radium-223 to bone metastases) while the disease remains well controlled with castration therapy. We hypothesised this combination would prove feasible and safe with a view to testing efficacy in a larger trial.

Patients and Methods

Study design and participants

We designed and implemented a prospective, single arm, open label phase I/II clinical trial at a single UK academic cancer center. Eligible patients had recently been diagnosed with histologically confirmed *de-novo* bone-metastatic mHSPC and had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1; all participants had at least three separate bone metastases demonstrated on technetium bone scan and no visceral metastases on CT thorax/abdo/pelvis. All patients were receiving long term LHRHa and were completing up to 6 cycles of upfront docetaxel (unless contraindicated) as standard of care prior to initiation of trial treatments. All patients were required to have no contraindication to pelvic radiotherapy or radium-223 treatment. Our recruitment target of 30 patients was based on an unacceptable rate of grade 3/4 bladder and bowel toxicity being ≥20%. Formal power calculations were not attempted due to single arm, noncomparative, phase I/II design. This target was felt to be a pragmatic target capable of identifying an unacceptable rate of toxicity as defined as greater than 20% grade 3/4.

The trial was registered with EudraCT (catalog. no. 2014–000273–39) and was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Ethical approval was obtained from the Northern Ireland Research Ethics Committee; all participants received written study information and provided written informed study consent. Full details are contained within the trial protocol. CONSORT diagram of trial profile is contained in Supplementary Data Supplementary Fig. S1. A trial management group met regularly to coordinate all aspects of the trial. An independent data monitoring committee oversaw the safety data.

Procedures

All patients were established on LHRHa prior to trial entry and continued this throughout the duration of the study. All docetaxel was completed prior to commencement of study treatments plus a post-docetaxel "wash-out" period of 6 weeks before trial treatments commenced. Radiotherapy was delivered at a dose of 74 Gy in 37 fractions to prostate and 60 Gy in 37 fractions to pelvic lymph nodes as simultaneous integrated boost. Patients were planned lying supine with full bladder and rectum empty by means of a microenema given prior to planning and delivery of each fraction of treatment (except for 2 days following radium-223 administration to limit risk of radiation exposure from faecal contamination). Prostate planning target volume (PTVp) consisted of prostate and base of seminal vesicles with a 7-mm margin posteriorly and 10-mm margin in other directions. Pelvic lymph node planning target volume (PTVln) was formed using a vessel expansion method previously described by the PIVOTAL clinical trial protocol (26).

Radium-223 was delivered at an activity of 55kBq/kg q28 days by slow intravenous injection for a total of 6 cycles. Day 1 cycle 1 of radium-223 was scheduled to coincide with day 1 of EBRT. Patients had radiotherapy doses or volumes amended to meet organ at risk (OAR) constraints if required. Patients were assessed prior to each cycle of radium-223; no dose reduction was permitted but each cycle could be delayed by up to 4 weeks to allow for resolution of toxicity. Any delay beyond 4 weeks led to radium-223 being discontinued.

Endpoints

Primary endpoints were feasibility, toxicity, and quality of life associated with the treatment. Feasibility was defined as being able to recruit 30 patients in a 2-year time frame from trial opening. The study safety data were reviewed by the trial management group monthly. Study stopping criteria in relation to toxicity were: two or more toxicity events at grade ≥ 4 lasting more than 7 days and deemed to be related to treatment; two or more nonhematologic toxicity events at grade ≥ 3 lasting >more than 10 days and deemed to be related to treatment; any grade 5 adverse event. Toxicities were assessed from trial consent until 8 weeks after final radium-223 infusion using Common Terminology Criteria for Adverse Events (CTCAE) v 4.03 (27). Following publication of the ERA-223 (28) data showing an excess of fractures in the combination radium-223+abiraterone group, the protocol was amended to additionally collect fracture data out to 2 years post initiation of treatment. Any fractures which occurred were classified as either malignant, nonmalignant traumatic, or nonmalignant fragility. This included all fractures seen on any imaging modality whether symptomatic or not. Symptomatic skeletal events were defined as: malignant spinal cord compression, symptomatic malignant fracture, radiotherapy, or surgical intervention for skeletal symptoms. Hematologic function was assessed with blood draws q4-weekly during treatment, 8 weeks post final radium-223 infusion and again at 6 months post final radium-223 infusion. Patient reported quality of life was assessed during treatment and until 6 months after final radium-223 infusion using the expanded prostate cancer index composite (EPIC; ref. 29).

Secondary endpoints included radiological [whole-body MRI (WB-MRI)] and biochemical [Prostate Specific Antigen (PSA) and Alkaline Phosphatase (ALP)] response. Whilst WB-MRI is a more recently developed and less well studied imaging modality than bone scintigraphy, it was chosen as the modality of choice given its ability to examine individual lesion response, rather than simply appearance of new lesions as in PCWG2 guideline for use of scintigraphy (30). All patients had a WB-MRI scan performed at screening, at 8 weeks post final radium-223 infusion and again at 6 months post final radium-223 infusion. T1, T2, and STIR sequences were performed on a General Electric Sigma Explorer 1.5 Tesla MRI scanner (GE Healthcare). A single independent consultant radiologist, with subspecialty

Table 1. Baseline details of trial population.

Demographic	Median (IQR) or *n* (%) unless stated
Age (years)	64 (59–68)
Range	45–82
WHO Performance status	
0	16 (53.3)
1	14 (46.7)
Significant comorbidities	
Ischemic heart disease	3 (10)
COPD	1 (3.3)
Atrial fibrillation	1 (3.3)
Pulmonary embolism	2 (6.7)
Hypertension	14 (46.7)
NIDDM	2 (6.7)
ISUP grade group	
3	2 (6.7)
4	7 (23.3)
5	20 (66.7)
Unclassified	1 (3.3)
PSA pre-ADT (ng/mL)	279.5 (58.6–1,076)
Range	10.49–5,844
T stage at diagnosis	
T1	1 (3.3)
T2	1 (3.3)
T3	18 (60)
T4	7 (23.3)
Tx	3 (10)
N stage at diagnosis	
N0	8 (26.7)
N+	17 (56.7)
Nx	5 (16.7)
Volume of disease (CHAARTED defn; ref. 8)	
High	24 (80)
Low	6 (20)
Docetaxel received (no cycles)	
0	2 (6.7)
4–6	28 (93.3)

experience in musculoskeletal and prostate MRI, assessed and reported all available scans. Scans were compared pairwise within each patient, screening to post cycle 6 radium-223 and post cycle 6 to end of study. Scans were reported in categorical fashion based on overall disease behavior showing: tumor burden (TB) increase, TB stable, TB reduction, TB resolution. TB 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 TB. TB reduction was indicated by a 50% decrease in 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 tumoral response. Stability fell between these definitions. TB resolution was indicated by complete resolution of lesions.

All patients had PSA and ALP measured q4 weekly during treatment, at 8 weeks post final radium-223 infusion and again at end of study, 6 months post final radium-223 infusion. Biochemical endpoints were, response in ALP and time to PSA progression defined by PCWG2 criteria: 25% or greater increase and an absolute increase of 2 ng/mL or more from the nadir (30).

Survival status was recorded at the time each study visit was due. Additionally, for patients alive at the end of study visit, remote review was performed every 3 months for 2 years post end of study visit to document survival.

Analysis and statistics

Feasibility and toxicity results are expressed as rates. Hematologic parameters are expressed as means per time point and paired sample *t* tests compare means across timepoints. PSA and ALP are expressed as means per time-point. Time taken to biochemical failure and OS is calculated using standard Kaplan–Meier methods; to account for the heterogeneity of the group (some of whom had pretrial docetaxel and some had not), survival is measured from delivery of first cycle of docetaxel or date of trial registration (if docetaxel omitted). EPIC quality of life results were transformed according to the published, validated matrix and are expressed as numerical scores (29); paired sample *t* tests compare mean scores across time-points.

Results

Patients were recruited between February 2016 and April 2019. At the time of data lock, median follow-up was 42 months. All patients had ECOG PS = 0 (53.3%) or 1 (46.7%). Median initial PSA prior to ADT was 279.5 ng/mL (Range 10.49 ng/mL to 5844 ng/mL). Two-thirds of patients had International Society of Urological Pathology (ISUP) grade group = 5 cancer. 25 patients (83.3%) had T3 or T4 disease and per CHAARTED (8) definition, 24 (80%) patients had high volume metastatic disease i.e., the presence ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis (no patients had visceral disease). 31 patients were allocated to study treatment; 1 patient progressed rapidly and proceeded to SOC treatment for mCRPC without having received any study treatments (Supplementary Fig. S1). Demographic and baseline data of treated patients are summarized in **Table 1**.

Table 2. Adverse events in those domains most commonly affected by toxicity – GI, GU, and hematologic.

	All grades *N* (%)	Grade 1 *N* (%)	Grade 2 *N* (%)	Grade 3 *N* (%)
Gastrointestinal				
Abdominal pain	9 (30)	8 (26.7)	1 (3.3)	–
Anorexia	4 (13.3)	4 (13.3)	–	–
Constipation	4 (13.3)	4 (13.3)	–	–
Diarrhea	25 (83.3)	19 (63.3)	6 (20)	–
Flatulence	2 (6.7)	2 (6.7)	–	–
Frequency and urgency	7 (23.3)	7 (23.3)	–	–
GI infection	1 (3.3)	–	1 (3.3)	–
Nausea/vomiting	9 (30)	8 (26.7)	1 (3.3)	–
Rectal bleeding	8 (26.7)	8 (26.7)	–	–
Urologic				
Dysuria	17 (56.7)	15 (50)	1 (3.3)	1 (3.3)
Hematuria	1 (3.3)	1 (3.3)	–	–
Nocturia	18 (60)	12 (40)	6 (20)	–
Frequency	9 (30)	8 (26.7)	1 (3.3)	–
Hesitancy	5 (16.7)	5 (16.7)	–	–
Incontinence	1 (3.3)	–	1 (3.3)	–
Urinary infection	1 (3.3)	–	–	1 (3.3)
Urgency	6 (20)	5 (16.7)	1 (3.3)	–
Hematologic				
Anemia	14 (46.7)	12 (40)	2 (6.7)	–
Neutropenia	22 (73.3)	13 (43.3)	8 (26.7)	1 (3.3)
Thrombocytopenia	8 (26.7)	7 (23.3)	–	1 (3.3)
Leukopenia	27 (90)	9 (30)	15 (50)	3 (10)

Treatments received

All patients had radiotherapy of between 70 and 74 Gy planned for the prostate in 35–37 fractions. One patient terminated radiotherapy early due to bladder toxicity having received 30 fractions of 2 Gy to the prostate. One patient received radiotherapy to prostate only (not pelvic lymph nodes) because small bowel constraints could not be met; 29 patients received between 50 and 60 Gy to the pelvic nodal PTV. Twenty-seven patients (90%) completed planned 6 cycles of radium-223. Three patients (10%) discontinued radium-223 at cycle 5.

Adverse events

During the 6 months of treatment and 8-week follow-up period, grade 1–3 adverse events occurred predominantly in the gastrointestinal (GI), urological (GU) and hematologic domains. No grade 4 or 5 toxicity was seen. Twenty-five patients (83.3%) experienced diarrhea, which was grade 1–2 in all patients. Seventeen patients (56.7%) experienced dysuria, this was grade 3 in 1 patient. One additional patient experienced a grade 3 urinary tract infection (UTI) which responded to antibiotic therapy. Three patients (10%) experienced grade 3 leukopenia; 1 each additional patient (3.3%) experienced grade 3 neutropenia and thrombocytopenia. These grade 3 hematologic events were all asymptomatic, there was no thrombocytopenia associated bleeding and no instances of neutropenic sepsis occurred. Adverse events in the domains GI, GU, and hematologic are detailed in **Table 2**; other adverse events are listed by grade in Supplementary Data Table S1.

Time scale of toxicity

Patients had blood drawn at screening, on day 0 of each cycle of radium-223, at 8 weeks post final cycle of radium-223 and 6 months later at end of study. Mean blood indices by time-point are shown in **Fig. 1** below. There is a significant reduction in all

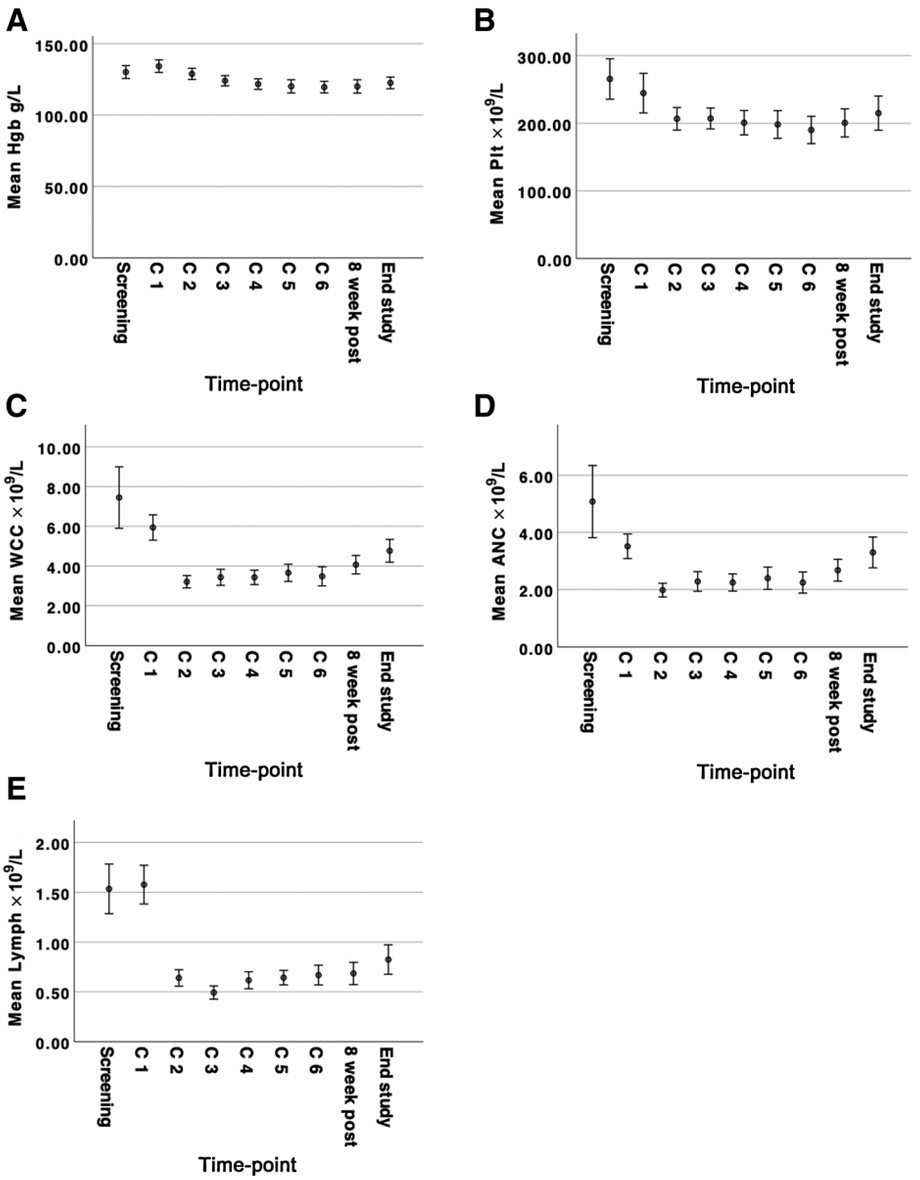

Figure 1.
Change in hematologic parameters during trial. Hemoglobin (Hgb; **A**), platelets (Plt; **B**), total white cell count (WCC; **C**), absolute neutrophil count (ANC; **D**), absolute lymphocyte count (Lymph; **E**). Values shown are mean with error bars 95% CI, time-points are screening, cycle 1 to 6 radium-223, 8 weeks post cycle 6 radium-223 and 6 months later at end of study.

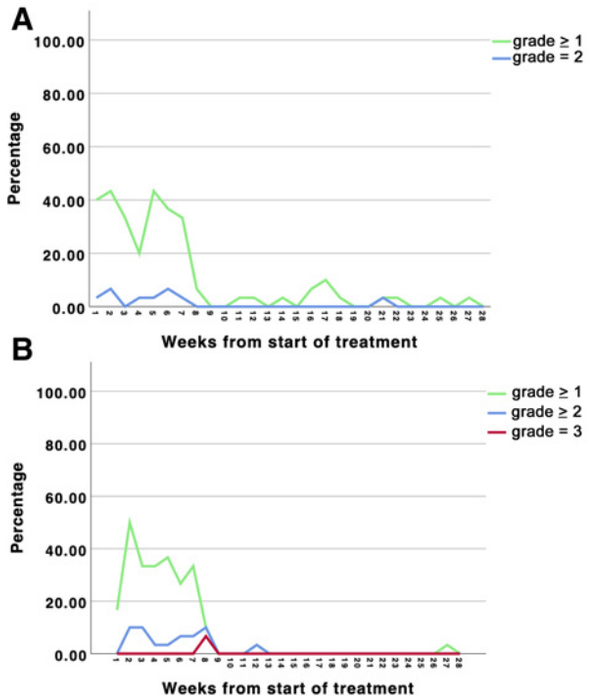

Figure 2.
Prevalence of CTCAE GI (**A**) and GU (**B**) toxicity grade ≥ 1, ≥ 2, ≥ 3 at weeks 1 to 28 during trial.

mean blood indices between screening and end of study (Hgb 131.4 g/L to 122.5 g/L $P = 0.001$; Plt 266.9 $\times$ 10^9/L to 215.0 $\times$ 10^9/L $P = 0.002$; WCC 7.8 $\times$ 10^9/L to 4.8 $\times$ 10^9/L $P < 0.001$; ANC 5.3 $\times$ 10^9/L to 3.3 $\times$ 10^9/L $P = 0.005$; Lymph 1.6 $\times$ 10^9/L to 0.8 $\times$ 10^9/L $P < 0.001$).

Figure 2 shows the prevalence of GI and GU toxicity during weeks 1–28 of trial (weeks 1–8 involve concurrent radiotherapy and radium-223). Grade 1–2 GI and GU toxicity is relatively common during the concurrent treatment phase, but prevalence of toxicity declines after EBRT completes and radium cycles continue.

Quality of life

Patients completed EPIC (29) scores at screening, q4 weekly during radium-223 treatment, at 8 weeks post final radium-223 treatment and 6 months later at end of study; mean domain scores are shown in Supplementary Data (Supplementary Fig. S2). There is a significant fall in bowel and urinary scores between screening and start of cycle 3, that is, during the concurrent phase of treatment (mean bowel score screening = 95.10, mean bowel score C3 = 81.0 $P < 0.001$; mean urinary score screening = 90.48, mean urinary score C3 = 79.02 $P = 0.003$). These scores recover such that there is no significant difference between scores at screening and scores at end of trial in either domain.

Markers of response and skeletal health

ALP responses are shown in waterfall plots, **Fig. 3A** and **B**. Between screening and cycle 6 radium-223, ALP fell in 27 patients (90%). This trend reverses 6 months later at end of study; at this time-point 15 patients (50%) have shown ALP increase relative to screening. WB-MRI responses are shown in **Fig. 3C** and **D**. In comparing WB-MRI between screening and post C6 radium-223, 24 patients (80%) had evidence of TB being stable or reduced. By the end of study, stable or reduced TB was maintained in 17 patients (56.6%). Supplementary Data (Supplementary Fig. S3) shows exemplar images detailing MRI evidence of reduced TB (Supplementary Fig. S3A–D) and increased TB (Supplementary Fig. S3E and S3F).

Median progression free survival was 20.5 months calculated by standard Kaplan–Meier methods. Median OS has not yet been reached. Survival curves are shown in Supplementary Data (Supplementary Fig. S4).

Patients were followed up for skeletal related outcomes for 2 years following treatment. During the trial no patients received bone health agents, as was standard for mHSPC patients at the time. In terms of fractures, in total 8 patients (26.7%) experienced at least one malignant fracture; 3 patients (10%) 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 impending spinal cord compression. **Table 3** summarizes skeletal related outcomes.

Discussion

This is the first published use of concurrent pelvic radiotherapy and radium-223 to treat metastatic prostate cancer. We demonstrated that the combination of ADT, upfront docetaxel, radium-223, and EBRT to prostate and pelvis is well tolerated and feasible in men with mHSPC metastatic to bone.

The treatment schedule was well tolerated with acceptable toxicity and impact on quality of life. The most common domains of toxicity were GI, GU, and hematologic. Diarrhea was common (25 of 30 patients) but the majority of patients experienced grade 1 toxicity only. No grade ≥ 3 GI toxicities occurred. One patient experienced grade 3 dysuria and 1 patient experienced a grade 3 UTI. GI and GU toxicity predominantly occurred within the first 8 weeks of treatment, i.e., during the phase of EBRT. The PIVOTAL trial (26) provides a comparator of a similar pelvic radiotherapy strategy being utilized without any additional radionuclide (although acute toxicity was reported on RTOG scales, unlike CTCAE scale in our study). In the group of patients receiving prostate and pelvic radiotherapy they found peak grade ≥2 acute GI toxicity in 26% patients compared with 7% in ADRRAD; peak grade ≥2 acute GU toxicity occurred in 40% of patients compared with 14% in ADRRAD. Therefore, the GI and GU toxicity in ADRRAD is in agreement with that seen in trials of modern radiotherapy alone to prostate and pelvis; there is no evidence of a synergistic increase in pelvic toxicity as a result of the concurrent administration of radium-223. These toxicities impact transiently on quality of life; with a significant drop in quality of life in urinary and bowel domains, which corrects back to baseline upon discontinuation of pelvic radiotherapy. Sexual and hormonal quality-of-life domains are relatively low at all trial time-points as a consequence of the well-established toxicity profile of LHRHa.

Bone marrow suppression is a recognized toxicity of radiotherapy involving bone marrow exposure. It is a particularly common toxicity of radionuclide therapies being used to target bone metastases, where the crossfire of radiation into the bone marrow compartment may be significant (24). Hematologic toxicity occurred at a higher rate in ADRRAD than in ALSYMPCA, the phase III trial of radium-223 used alone in mCRPC. All grades anemia, thrombocytopenia, and neutropenia occurred at rates of 46.7%, 26.7%, and 73.3% respectively in ADRRAD compared with 31%, 12%, and 5% in ALSYMPCA (25). There is a trend to slow resolution in marrow suppression upon

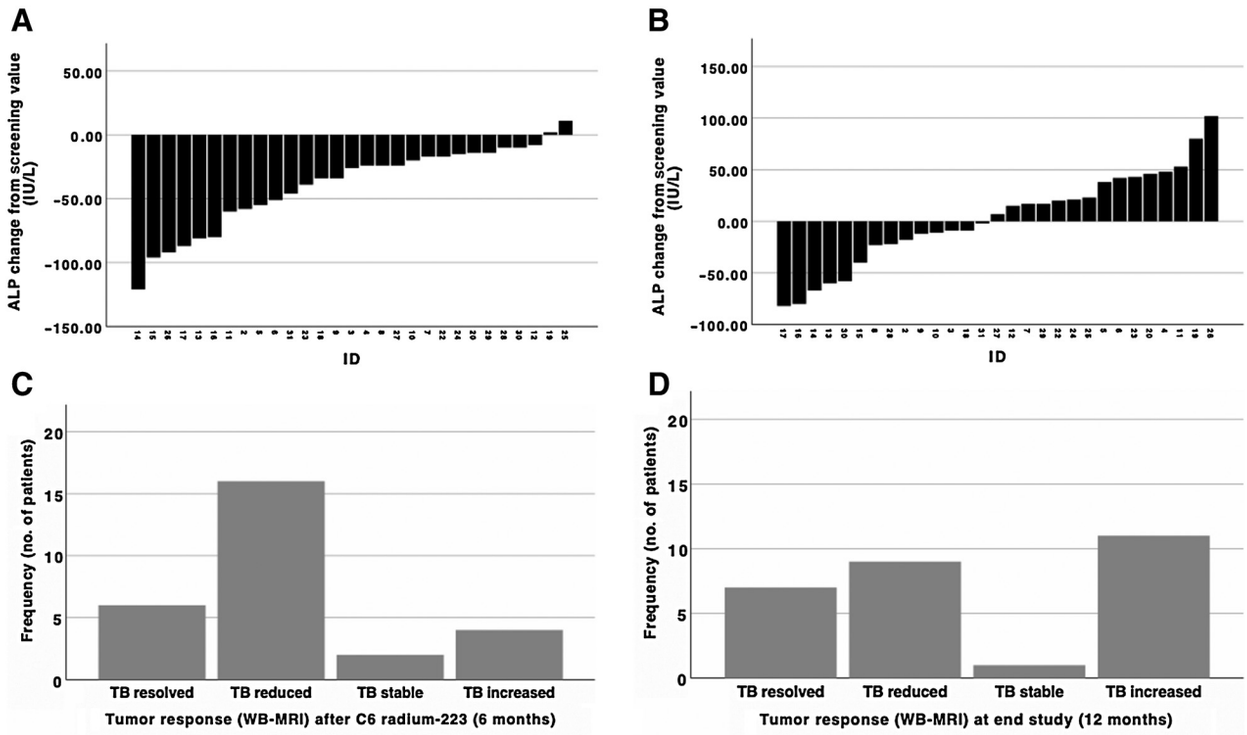

Figure 3.

Plots showing markers of disease response. **A,** Waterfall plot showing change in ALP from screening to cycle 6 radium-223. **B,** Waterfall plot showing change in ALP from screening to end of study (IU/L). **C,** Histogram showing change in TB on MRI between screening and cycle 6 radium-223. **D,** Histogram showing change in TB on MRI between screening and end of study. **C** and **D,** MRI change is grouped into discrete categories: TB resolved, TB reduced, TB stable, TB increased. *Y*-axis details number of patients in each category.

cessation of therapy (**Fig. 1**) but hemoglobin, platelet, white cell, lymphocyte, and neutrophil counts all remain statistically significantly lower at completion of study than at screening. Although this hematologic toxicity is common, it is predominantly low grade; no clinical sequelae were reported related to it and in particular no instances of neutropenic sepsis occurred. There does not appear to be any difference in hematologic toxicity experienced by volume of disease; although numbers are small ($n = 6$ with low volume disease), the same trends occur in both groups and there is no statistically significant difference in mean blood parameters at any time point between low and high volume metastases groups. The reasons for this degree of bone marrow suppression are unclear. The marrow radiation dose from prostate and pelvic radiotherapy has been recognized, in this study pelvic marrow was not treated as an organ at risk. Additionally, the majority (93.3%) of patients had recently completed 4–6 cycles of docetaxel before commencing study. Per protocol, all patients had to have a 6-week washout between final cycle docetaxel and commencing study treatments, the median time was 13 weeks. Although they had normal hematologic function to enter study, there may be residual bone marrow stress from chemotherapy which results in the heightened rates of hematologic toxicity shown in this study. Previous subgroup analysis has confirmed the acceptable toxicity profile of radium-223 in patients who have received prior docetaxel (31); this study in predominantly (93.3%) postdocetaxel patients has shown the combination of radium-223 + EBRT to be well tolerated regardless of prior docetaxel.

Although this phase I/II trial was noncomparative, there are signs suggesting anticancer efficacy of the combination. Twenty-seven

Table 3. Summary of skeletal-related outcomes.

	Outcome		Count
Malignant	SSE (10 events)	Palliative XRT for skeletal symptoms	8 courses (4 patients)
		Palliative XRT for impending spinal cord compression	1 course
		Symptomatic malignant fracture not receiving XRT	1 fracture
	Non-SSE (9 events)	Asymptomatic malignant fracture	9 events
			19 fractures, (7 patients)
Nonmalignant		Traumatic fracture	2 fractures (1 patient)
		Fragility fracture	3 fractures (3 patients)

patients (90%) demonstrated a decrease in ALP between screening and cycle 6. This was accompanied by 24 patients (80%) demonstrating either stable or reduced TB on WB-MRI scan between screening and completion of cycle 6 radium-223. Some dramatic MRI examples of resolution of skeletal metastases were seen (Supplementary Fig. S3). It is impossible with the current study design to separate late responses to LHRHa +/- docetaxel from responses to study treatments. However the ALP changes, coupled to the MRI improvements seen in a subgroup of patients at the later time point (>1 year post last docetaxel) suggest certain patients derive real anticancer benefit from the combination.

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; it also allows comparison with other trials in mHSPC. Biochemical progression free survival = 20.5 months in this population with predominantly high volume disease (80%). These results are very encouraging in the context of results from the STAMPEDE mHSPC cohort treated with docetaxel; in an unplanned subgroup analysis clustering by volume of disease, the failure free survival for the high volume group was just over 1 year (32). As shown in Supplementary Fig. S1, 1 patient progressed rapidly into mCRPC and did not receive study treatments which may positively skew our data with reference to STAMPEDE.

The effect of radium-223 on overall skeletal health has been a subject of some debate. The original ALSYMPCA trial (25) demonstrated that radium-223 significantly prolonged the time to first symptomatic skeletal event from 9.8 months to 15.6 months $P < 0.001$. More recently, the ERA-223 randomized controlled trial combining radium-223 with abiraterone was unblinded early due to concerns about increased rates of fracture and death in the combination. Fractures occurred in 29% of the combination group compared with 11% of the placebo (abiraterone alone) group (28). In ADRRAD 15 adverse events occurred relating to fracture. The majority of these (9 events) were asymptomatic pathological fractures picked up on imaging alone. One symptomatic pathological fracture occurred. One patient sustained two fracture events which were clearly related to trauma. Three patients sustained fragility fractures – that is fractures in sites of bone without metastases but with no history of trauma to explain the fracture. These were two vertebral fractures and one sacral ala fracture. The effect of LHRHa in reducing bone mineral density is well established (33), pelvic radiotherapy may also predispose to sacral insufficiency fractures (34). So whilst the underlying rate of fractures appears high at 15 events, it is unclear at this stage if there is an excess fracture risk attributable to radium-223 or whether it simply represents the combined effects of metastases causing pathologic fractures and other treatments contributing to osteoporosis. None of the patients in this study received bone health agents, as was the clinical standard for mHSPC at the time. In light particularly of the ERA-223 study, such agents would likely be encouraged or mandated in future phase III trials.

Translational assays were built into the trial looking at circulating tumor cell numbers, markers of DNA damage in circulating tumor cells and lymphocytes and positivity for a previously published 44 gene microarray identifying deficiencies in DNA damage repair (35). These results are pending.

Prostate radiotherapy has become established as a standard of care for patients with mHSPC and low volume disease. Radium-223 remains a standard of care treatment for patients with mCRPC. Additionally, next generation radionuclides are in development. Early data have been promising for Lutetium-177/PSMA conjugates (36) and further trials continue. It seems likely that in metastatic prostate cancer there will continue to be a role for radiotherapy to target prostate and radionuclide therapy to target areas of more disseminated metastases. This trial demonstrates for the first time the feasibility of combining these modalities and shows early signals of efficacy which will continue to be investigated in future trials.

Future work surrounds completion of the translational science analysis and the design of a phase III randomized control trial testing formally the efficacy of the combination.

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Authors' Contributions

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References

1. Rawla P. Epidemiology of prostate cancer. World J Oncol 2019;10:63–89.
2. Northern Ireland Cancer Registry. Official statistics: prostate cancer. Available from: http://www.qub.ac.uk/research-centres/nicr/CancerInformation/official-statistics/BySite/Prostate.
3. James ND, Spears MR, Clarke NW, Dearnaley DP, De Bono JS, Gale J, et al. Survival with newly diagnosed metastatic prostate cancer in the "Docetaxel Era": Data from 917 patients in the control arm of the STAMPEDE Trial (MRC PR08, CRUK/06/019). Eur Urol 2014;67:1028–38.
4. Carlin BI, Andriole GL. The natural history, skeletal complications, and management of bone metastases in patients with prostate carcinoma. Cancer 2000;88: 2989–94.
5. Lange PH, Vessella RL. Mechanisms, hypotheses and questions regarding prostate cancer micrometastases to bone. Cancer Metastasis Rev 17:331–6.
6. Schally AV. Luteinizing hormone-releasing hormone analogs: their impact on the control of tumorigenesis. Peptides 1999;20:1247–62.
7. James ND, Sydes MR, Clarke NW, Mason MD, Dearnaley DP, Spears MR, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet 2016;387: 1163–77.
8. Sweeney CJ, Chen YH, Carducci M, Liu G, Jarrard DF, Eisenberger M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med 2015;373:737–46.
9. James ND, de Bono JS, Spears MR, Clarke NW, Mason MD, Dearnaley DP, et al. Abiraterone for prostate cancer not previously treated with hormone therapy. N Engl J Med 2017;377:338–51.
10. Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med 2017;377:352–60.
11. Davis ID, Martin AJ, Stockler MR, Begbie S, Chi KN, Chowdhury S, et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. N Engl J Med 2019;381:121–31.
12. Armstrong AJ, Szmulewitz RZ, Petrylak DP, Villers A, Azad A, Alcaraz A, et al. Phase III study of androgen deprivation therapy (ADT) with enzalutamide (ENZA) or placebo (PBO) in metastatic hormone-sensitive prostate cancer (mHSPC): The ARCHES trial. J Clin Oncol 2019;37:687.
13. Chi KN, Agarwal N, Bjartell A, Chung BH, Pereira de Santana Gomes AJ, Given R, et al. Apalutamide for metastatic, castration-sensitive prostate cancer. N Engl J Med 2019;381:13–24.
14. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351:1502–12.
15. Ryan CJ, Smith MR, Fizazi K, Saad F, Mulders PFA, Sternberg CN, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 16:152–60.
16. Logothetis CJ, Basch E, Molina A, Fizazi K, North SA, Chi KN, et al. Effect of abiraterone acetate and prednisone compared with placebo and prednisone on pain control and skeletal-related events in patients with metastatic castration-resistant prostate cancer: exploratory analysis of data from the COU-AA-301 randomised trial. Lancet Oncol 2012;13:1210–7.
17. Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014;371:424–33.
18. Scher HI, Fizazi K, Saad F, Taplin M-E, Sternberg CN, Miller K, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012;367:1187–97.
19. Smith MR, Saad F, Chowdhury S, Oudard S, Hadaschik BA, Graff JN, et al. Apalutamide treatment and metastasis-free survival in prostate cancer. N Engl J Med 2018;378:1408–18.
20. Dearnaley D, Syndikus I, Mossop H, Khoo V, Birtle A, Bloomfield D, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. Lancet Oncol 2016;17:1047–60.
21. Widmark A, Klepp O, Solberg A, Damber JE, Angelsen A, Fransson P, et al. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. Lancet 2009 Jan 24;373:301–8.
22. Warde P, Mason M, Ding K, Kirkbride P, Brundage M, Cowan R, et al. Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial. Lancet 2011;378:2104–11.
23. Parker CC, James ND, Brawley CD, Clarke NW, Hoyle AP, Ali A, et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. Lancet 2018;392: 2353–66.
24. Turner PG, O'Sullivan JM. (223)Ra and other bone-targeting radiopharmaceuticals-the translation of radiation biology into clinical practice. Br J Radiol 2015; 88:20140752.
25. Parker C, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, Fosså SD, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med 2013;369:213–23.
26. Dearnaley D, Griffin CL, Lewis R, Mayles P, Mayles H, Naismith OF, et al. Toxicity and patient-reported outcomes of a phase 2 randomized trial of prostate and pelvic lymph node versus prostate only radiotherapy in advanced localised prostate cancer (PIVOTAL). Int J Radiat Oncol Biol Phys 2019;103:605–17.
27. NCI. Common Terminology Criteria for Adverse Events v4.03. 4.03; 2010.
28. Smith M, Parker C, Saad F, Miller K, Tombal B, Ng QS, et al. Addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (ERA 223): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2019;20: 408–19.
29. Wei JT, Dunn RL, Litwin MS, Sandler HM, Sanda MG. Development and validation of the expanded prostate cancer index composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. Urology 2000;56:899–905.
30. Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 2008;26:1148–59.
31. Hoskin P, Sartor O, O'Sullivan JM, Johannessen DC, Helle SI, Logue J, et al. Efficacy and safety of radium-223 dichloride in patients with castration-resistant prostate cancer and symptomatic bone metastases, with or without previous docetaxel use: a prespecified subgroup analysis from the randomised, double-blind, phase 3 ALSYMPC. Lancet Oncol 2014;15:1397–406.
32. Clarke NW, Ali A, Ingleby FC, Hoyle A, Amos CL, Attard G, et al. Addition of docetaxel to hormonal therapy in low- and high-burden metastatic hormone sensitive prostate cancer: long-term survival results from the STAMPEDE trial. Ann Oncol Off J Eur Soc Med Oncol 2019;30:1992–2003.
33. Rachner TD, Coleman R, Hadji P, Hofbauer LC. Bone health during endocrine therapy for cancer. Lancet Diabetes Endocrinol 2018;6:901–10.
34. Bazire L, Xu H, Foy J-P, Amessis M, Malhaire C, Cao K, et al. Pelvic insufficiency fracture (PIF) incidence in patients treated with intensity-modulated radiation therapy (IMRT) for gynaecological or anal cancer: single-institution experience and review of the literature. Br J Radiol 2017;90(1073):20160885.
35. Mulligan JM, Hill LA, Deharo S, Irwin G, Boyle D, Keating KE, et al. Identification and validation of an anthracycline/cyclophosphamide–based chemotherapy response assay in breast cancer. J Natl Cancer Inst 2014;106djt335.
36. Hofman MS, Violet J, Hicks RJ, Ferdinandus J, Thang SP, Akhurst T, et al. [(177) Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. Lancet Oncol 2018;19:825–33.