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Clinical Trial

Radium-223 for patients with metastatic castration-resistant prostate cancer with asymptomatic bone metastases progressing on first-line abiraterone acetate or enzalutamide: A single-arm phase II trial

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KEYWORDS
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Metastatic castration-resistant prostate cancer

Abstract ***Purpose:*** The paper aims to evaluate the efficacy and safety of ^{223}Ra in patients who progressed after first-line androgen deprivation therapy.
Patients and methods: EXCAAPE (NCT03002220) was a multicentre, single-arm, open-label, non-controlled phase IIa trial in 52 patients with metastatic castration-resistant prostate cancer and asymptomatic bone metastases who have progressed on abiraterone acetate or enzalutamide, up to six doses of ^{223}Ra (55 kBq/kg of body weight per month). The primary end-point was radiographic progression-free survival (rPFS). Secondary end-points included rPFS based on androgen receptor splice variant 7 (AR-V7) expression in circulating tumour cells (CTCs), overall survival, and safety.
Results: Median rPFS was 5.5 months (95% CI 5.3–5.5). Median rPFS of patients with AR-V7(−) CTCs was longer than that of patients with AR-V7(+) CTCs (5.5 versus 2.2 months, respectively; $P = 0.056$). Median overall survival was 14.8 months (95% CI 11.2–not reached) and was significantly greater for AR-V7(−) patients than for AR-V7(+) patients (14.8 months versus 3.5 months, respectively; $P < 0.01$). ^{223}Ra was well tolerated; anaemia and thrombocytopenia were the most common grade 3/4 adverse events (5.8% and 11.5%, respectively).
Conclusions: ^{223}Ra seems to be a reasonable treatment for patients with metastatic castration-resistant prostate cancer and asymptomatic bone metastases progressing on novel hormonal therapy and had an acceptable safety profile.

1. Introduction

Prostate cancer is the second most commonly diagnosed cancer worldwide and the fifth leading cause of cancer mortality in men [1]. Five-year survival rates of prostate cancer are poor when distant metastases are present [2,3], being bone the most common metastatic site [4].

The mainstay treatment for patients with advanced prostate cancer is conventional androgen deprivation therapy (ADT); however, most patients develop resistance to ADT, classified then as castration-resistant prostate cancer (CRPC) [5–7]. Docetaxel was the only treatment for patients with metastatic CRPC (mCRPC) until 2010; in the past decade, new agents have been approved, including novel hormonal therapy (e.g. abiraterone acetate, enzalutamide), next-generation taxanes (e.g. cabazitaxel), immunotherapy (sipuleucel-T), alpha particle-emitting agents (radium-223 [^{223}Ra]), and poly-ADP-ribose polymerase (PARP) inhibitors [5].

Treatment with the alpha particle-emitting bone-targeted radionuclide ^{223}Ra is recommended for treating bone-symptomatic mCRPC patients without visceral metastases prolonging overall survival (OS) and time to first symptomatic skeletal event, on the basis of the ALSYMPCA trial that led to its approval [8]. Moreover, a recent single-arm, phase IIIb trial found that ^{223}Ra with concomitant abiraterone, enzalutamide, or denosumab led to improved survival of patients with mCRPC with bone metastases (BMs); particularly, asymptomatic patients achieved better OS than symptomatic patients [9,10]. However, the randomised, phase III ERA 223 trial found that ^{223}Ra combined with abiraterone acetate plus prednisone or prednisolone did not prolong symptomatic skeletal event-free survival but rather led to an increase in the incidence of fractures compared with placebo, plus abiraterone acetate, prednisone, or prednisolone [11].

Patients may also develop resistance to novel hormonal therapy, which has been linked to androgen receptor splice variant 7 (AR-V7), among other causes [5]. AR-V7 expression is higher in prostate cancer compared to normal prostate tissue and significantly increased with the number of lines of therapy received [5,12]. AR-V7-positive expression in circulating tumour cells (CTCs) represents a strong independent predictor of poor outcome in patients treated with the second- and third-line next-generation hormonal therapies [13]. Clinical studies showed that patients with AR-V7-positive mCRPC will benefit more from taxane-containing regimens rather than additional hormonal therapies[14,15]. However, no data exist on AR-V7 expression as a predictor of outcomes in patients with mCRPC who received ^{223}Ra.

Given the paucity of data regarding asymptomatic patients, EXCAAPE study aimed to evaluate the efficacy and safety of ^{223}Ra in patients with mCRPC with asymptomatic BMs who have progressed on first-line abiraterone acetate or enzalutamide, with an interest in assessing its value as an alternative to docetaxel. The association between AR-V7 expression in CTCs and ^{223}Ra efficacy was also evaluated.

2. Patients and methods

2.1. Study design and patients

This multicentre, single-arm, open-label, non-controlled phase IIa was conducted at nine sites in Spain. Patients with mCRPC and asymptomatic BMs who progressed on first-line treatment with abiraterone acetate or enzalutamide were treated with up to six cycles (one every 4 weeks) of intravenous injections of 55 kBq/kg of body weight of ^{223}Ra per month. BMs were defined as asymptomatic when patients reported no pain in the previous 24 h and no use of opiate analgesics for prostate cancer-related pain at screening or in the 2 weeks prior. Adult patients with a histologically confirmed adenocarcinoma of the prostate, BMs, and no visceral metastases; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; who had received treatment with abiraterone acetate or enzalutamide ≥24 weeks and were receiving ADT; or had a bilateral orchiectomy were eligible. Full enrolment criteria can be found in the Supplementary Material.

The study protocol and all its amendments were approved by Ethics Committee of Clinical Research Parc Taulí (Spain). The trial was done in compliance with the Declaration of Helsinki, and all patients provided written informed consent before enrolment. This study was registered at ClinicalTrials.gov (NCT030022-20).

2.2. Outcomes

The primary end-point was radiographic progression-free survival (rPFS) using Prostate Cancer Clinical Trials Working Group 2 criteria. Timing of assessments is shown in Table S1. The secondary end-points included the assessment of AR-V7 expression in CTCs and CTC count at baseline and at disease progression or treatment completion; the analysis of OS based on AR-V7 expression in CTCs, time to first symptomatic skeletal event (SSE), PFS using Response Evaluation Criteria in Solid Tumors version 1.1, time to prostate-specific antigen (PSA) progression using Prostate Cancer Clinical Trials Working Group 2 criteria, PSA response (≥30% or ≥50% reduction from baseline at 12 weeks), and alkaline phosphatase (ALP) level of response using ALSYMPCA study criteria (<220 U per litre) [17]; the assessment of adverse events (AEs) using the Common Terminology Criteria for Adverse Events 4.0, vital signs, ECOG status, physical examination, duration and extent of exposure, concomitant medications, Brief Pain Inventory Questionnaire at baseline and quality of life of patients according to the functional assessment of cancer therapy for prostate questionnaire (FACT-P) at baseline, cycle 1 to cycle 6, and end of treatment (EoT).

2.3. Detection of CTCs

Blood samples were collected by venipuncture at the baseline and at the EoT when documenting disease progression. CTCs were detected by isolating nucleated cells from blood samples, carrying out immunofluorescence for counting rare cells using the Epic Sciences platform, as previously described [18]. Briefly, nucleated cells from blood samples were fixed onto glass pathology slides and stained for cytokeratin (CK) and CD45 by immunofluorescence. CTCs were identified as DAPI(+), CK(+), CD45(−) cells.

2.4. Determination of AR-V7 expression in CTCs

AR-V7 was determined as previously described [16,19]. Briefly, slides with fixed cells from blood samples were stained; candidate DAPI(+), CD45(−), CK(+) CTCs with nuclear expression of AR-V7 (Abcam EP343 clone, Abcam plc, Cambridge, UK) were scored and confirmed by trained technicians. A sample was considered AR-V7-positive if at least one CTC had nuclear AR-V7.

2.5. Statistical analysis

Primary analysis was based on a one-arm log-rank test (null hypothesis: rPFS ≤3 months; alternative: rPFS ≥6.3 months) [20]. A sample size of 52 patients was needed to attain 80% power at a nominal one-sided α level of 5%. The efficacy and safety analyses included all treated patients.

Kaplan–Meier and Clopper–Pearson methods were used to estimate 95% confidence intervals (CIs) for median survival and percentage, respectively. Wilcoxon test and 95% CIs for mean difference were used to analyse change between baseline and EoT for quantitative scores. In subgroup analyses, time-to-event end-points were analysed using the Firth's method for Cox regression model, due to low number of patients and unbalanced cohorts. Binary end-points were analysed using Chi-squared or Fisher's exact tests. Statistical analyses were conducted with R version 4.0.2.

3. Results

3.1. Patients and treatment

Between December 2016 and October 2018, 63 patients were screened. Of these, 52 met the eligibility criteria and were included in this study (Fig. S1; Table S2). Patients had a median age of 76.1 years; 48 (92.3%) had received two prior lines of hormone therapy (plus concomitant ADT), and 35 (87.5%) were negative for AR-V7 (Table 1).

Median duration of treatment was 5.5 months (1.3–6.4), and 40.4% (21/52) of the patients did not

Table 1
Patient demographics.

Characteristic	AR-V7 [+] N = 5	AR-V7 [-] N = 35	All patients N = 52
Age, median, (IQR), years	82.2 (79.0; 82.4)	74.7 (66.2; 83.0)	76.1 (69.4; 82.3)
PSA, median (IQR), µg/L	35.5 (6.4–317.4)	13.7 (0.5–703.3)	20.3 (0.04–703.3)
ALK, median (IQR), µg/L	105 (97.0–179)	118 (83.8–203)	113 (87.5–198)
Brief Pain Inventory			
Intensity, median (IQR)	0 (0–0.75)	0 (0–1.25)	0 (0–3)
Interference, median (IQR)	0 (0–2.4)	0 (0–7.3)	0 (0–7.3)
HRQoL Questionnaire (FACT-P)			
Median (IQR), U/L	117.6 (103–145)	119.3 (63.7–141.8)	120.5 (46.6–148)
Number of bone lesions, n (%)			
<6	1 (20)	10 (28.6)	15 (28.8)
6–20	4 (80)	24 (68.6)	36 (69.2)
>20	0 (0)	1 (2.8)	1 (2)
Prior lines of hormonal therapy in the castration-resistance setting, n (%)[a]			
Abiraterone	4 (80)	24 (68.6)	32 (61.5)
Enzalutamide	2 (40)	13 (37.1)	23 (44.2)
Abiraterone and enzalutamide[b]	1 (20)	3 (8.6)	4 (7.7)
Prior docetaxel in the hormone-sensitive setting, n (%)			
No	5 (100)	32 (91.4)	48 (92.3)
Yes	0 (0)	3 (8.6)	4 (7.7)

FACT-P: functional assessment of cancer therapy – prostate; HRQoL: health-related quality of life; IQR: interquartile range (percentile 25 to percentile 75).
[a] Hormonal therapy includes androgen deprivation therapy, abiraterone acetate, or enzalutamide.
[b] Patients 02-01, 02–05, 02–09, and 08-01 first received abiraterone and, after having discontinued treatment due to toxicity with no disease progression, they started treatment with enzalutamide.

complete all six cycles, mainly due to disease progression prior to the sixth cycle – other reasons were withdrawal of consent, discontinuation due to unacceptable toxicity, worsening of ECOG status, or investigator's decision.

3.2. Radiographic response and survival

At a median follow-up of 6.6 months (1.3–18.2), median rPFS was 5.5 months (95% CI 5.3–5.5; P = 0.025) meeting the primary end-point. Thirty-one (59,6%) of the 52 patients experienced progression disease or death (Table 2). Median rPFS of patients with AR-V7(–) CTCs was longer than that of patients with AR-V7(+) CTCs; however, the difference was not statistically significant (5.5 versus 2.2 months, respectively; P = 0.398; Fig. 1).

3.3. Secondary efficacy end-points

By data cut-off on January 9, 2021, 14 patients (26.9%) had died; median OS was 14.8 months (95%CI 11.2–not reached; Fig. 2). Subgroup analyses showed that OS was significantly longer for patients with AR-V7(–) expression compared to patients with AR-V7(+) expression (14.8 months versus 3.5 months, respectively; P < 0.01; Fig. 3).

Table 2
Location of disease radiological progression after ^{223}Ra therapy.

Variable, n (%)	N = 52
Without radiological progression	21 (40.4)
Radiological progression	31 (59.6)
Bone	21 (40.4)
Lymph nodes	11 (21.2)
Lung	3 (5.8)
Liver	2 (3.8)
Bladder	1 (1.9)

PSA levels significantly increased from baseline to EoT (mean difference 73.2; 95%CI 19.6–126.7; P < 0.001). No clinically relevant variation in vital signs was observed.

At baseline, 27 patients (51.9%) had ECOG 0 status and 25 (48.1%) had ECOG 1. At EoT, the number of patients with ECOG 0 significantly decreased (12; 23.1%, P < 0.01), whereas the number of patients with ECOG 1 remained stable (26; 50%). Moreover, ECOG 2 and ECOG 3 status were recorded (4 patients, 7.7%; and 5 patients, 9.6%, respectively).

Five patients experienced SSEs (9.6%); median time to first SSE was not reached (Fig. 3)

There was a confirmed PSA response, defined as a ≥30% or ≥50% reduction in PSA serum levels, in five (9.6%; 95%CI 3.2–21.0) and four patients (7.7%; 95%CI 2.1–18.5), respectively. Use of post-protocol therapy is reported in supplementary data (Table S3).

There was a confirmed ALP response, defined as ≥30% or ≥50% reduction in ALP serum levels, in 25 (48.1%; 95%CI 34.0–62.4) and 12 patients (23.1%; 95% CI 12.5–36.8), respectively.

3.4. CTC count before and after treatment

CTC count changed in some patients over the treatment course. A trend for association with OS can be observed but without statistical significance.

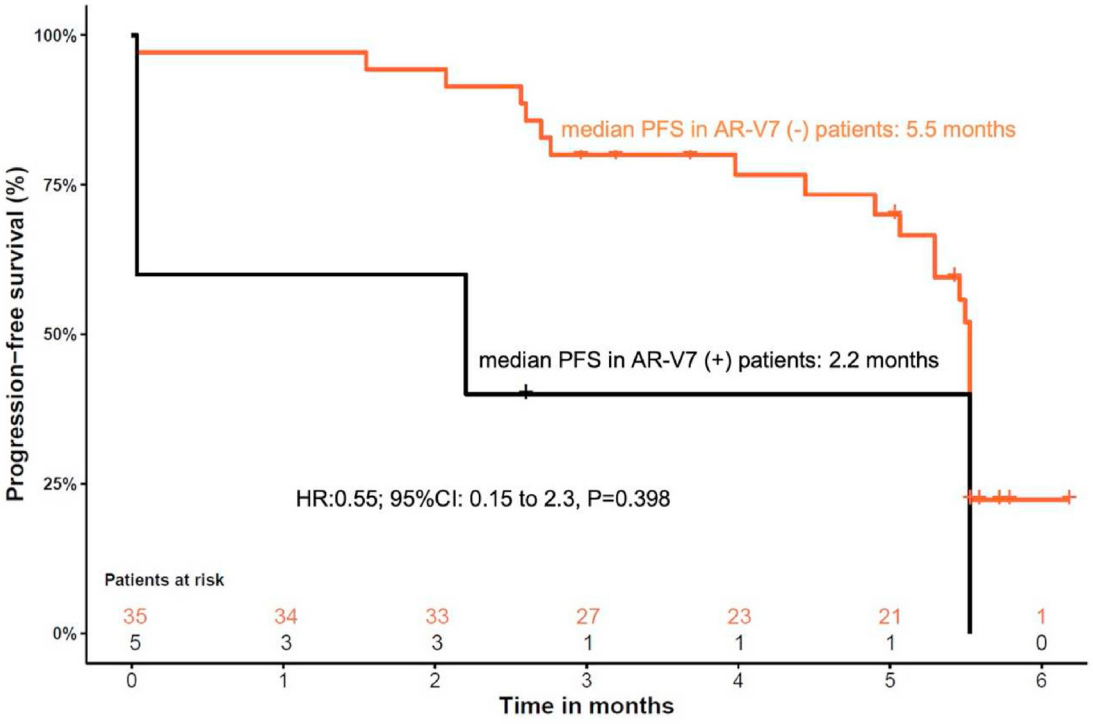

Fig. 1. **Radiographic progression-free survival based on AR-V7 expression.** Kaplan–Meier curves of radiographic progression-free survival, evaluated using Prostate Cancer Clinical Trials Working Group 2 criteria. Tick marks indicate censored data. Analyses adjusted by age, bone lesions, PSA, and AKT values at baseline. AR-V7: androgen receptor splice variant-7; CI: confidence interval; rPFS: radiographic progression-free survival.

Baseline and EoT CTC count were available for 21 patients. At baseline, most patient samples (30/40) had <5 CTCs. Of the seven patients with ≥5 CTCs at baseline who also had EoT evaluation, five had <5 CTCs at EoT. Of the 14 patients with <5 CTCs at baseline who also had EoT evaluation, only 1 had ≥5 CTCs at EoT (Table S4).

Patients who experienced a reduction in the number of CTCs from baseline to the EoT had a longer OS; however, the likelihood ratio test had P = 0.073 (Fig. S2).

3.5. AR-V7 expression in CTCs before and after treatment

Baseline AR-V7 expression in CTCs was not determined for 12 patients (23.1%) because of prolonged time between sample collection and processing (over 96 h). Thirty-five (87.5%) of the 40 patients showed no expression of AR-V7 in CTCs at baseline. Evaluation of 20 patients showed that two (10%) were positive for AR-V7 at baseline and switched to negative AR-V7, and only one who was negative at baseline became positive at the EoT (Table S4).

Patients who experienced a switch from a positive to a negative AR-V7 expression had a longer OS; however, the likelihood ratio test had P = 0.058 (Fig. S3).

3.6. Correlation between CTC count and AR-V7 expression before and after treatment

Baseline CTC count was available for 40 patients. Patients with negative AR-V7 expression showed lower CTC count than those with positive AR-V7 expression (1.3 [0.3–4.7] versus median 4.7 [IQR 3.5–7.3]); P = 0.074; Fig. S4).

EoT CTC count was available for 27 patients. Patients with negative AR-V7 expression showed lower CTC count than those with positive AR-V7 expression (median 0.5 [IQR 0.1–2.1] versus 2.5; Fig. S5).

3.7. Safety

Three deaths occurred, none treatment-related. Two patients discontinued treatment due to AEs (Table 3). Overall, 46 patients (88.5%) reported AEs; asthenia (26.9%) and arthralgia (25.0%) were the most common (Table S5). Anaemia and thrombocytopenia were the most common grade 3/4 AEs overall (5.8% and 11.5%, respectively) and possibly treatment-related AEs (3.8% in both cases). Serious AEs were reported by 11 patients (21.2%); the most common was anaemia (5.8%; Table S6).

4. Discussion

We established the efficacy and safety of ^{223}Ra for treating patients with mCRPC and asymptomatic BMs

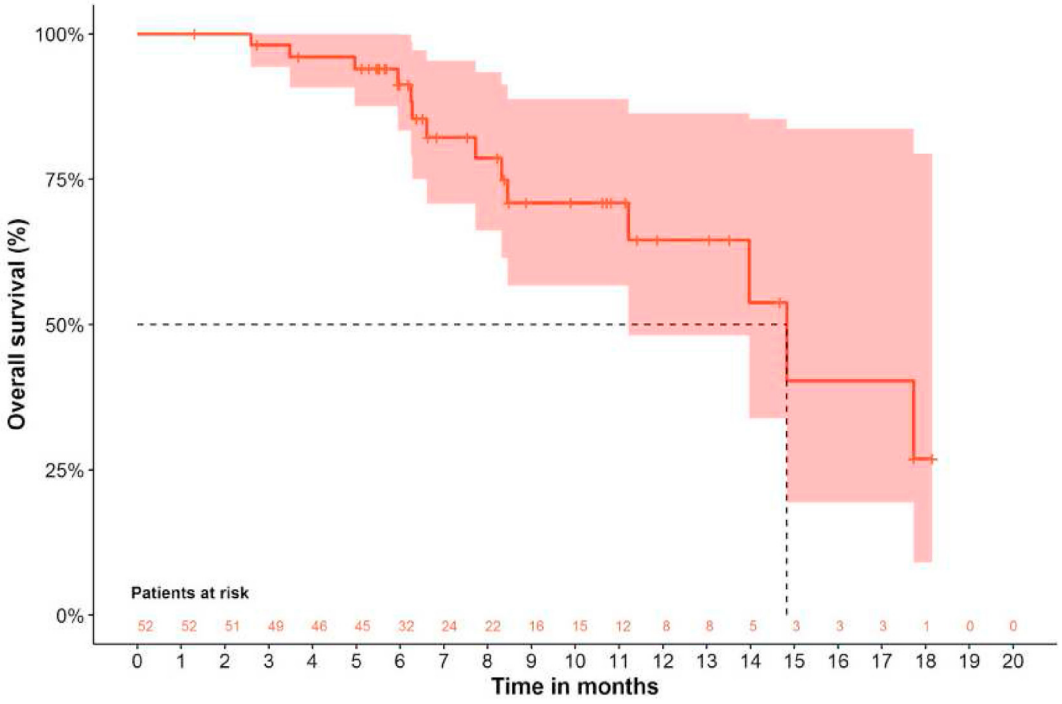

Fig. 2. **Overall survival Kaplan–Meier curve.** Kaplan–Meier curve of overall survival. Tick marks indicate censored data. CI: confidence interval; OS: overall survival; NE: not evaluable.

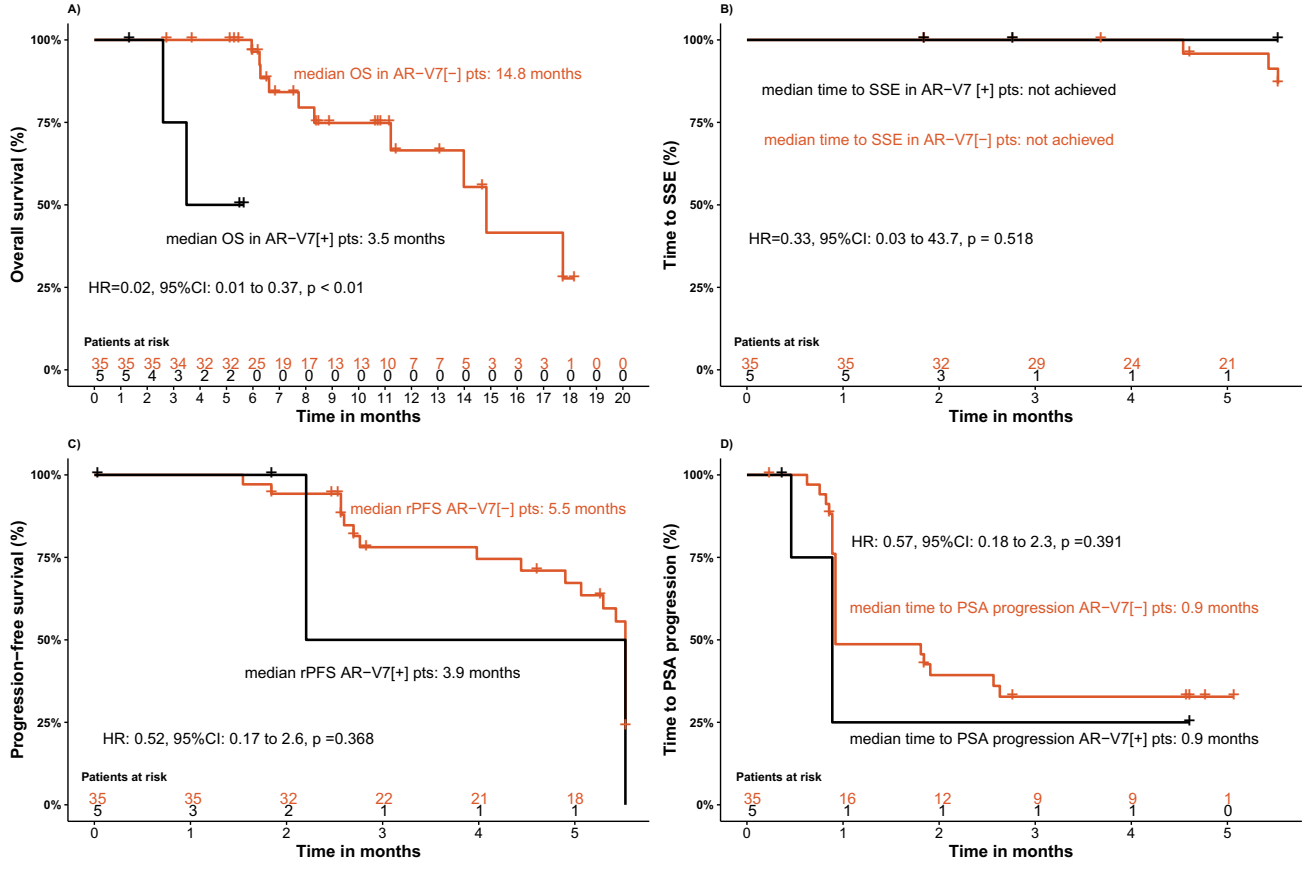

Fig. 3. **Kaplan–Meier curves of time-to-event end-points subgroup analysis based on AR-V7 expression.** (A) Overall survival. **(B)** Time to the first symptomatic skeletal event (SSE). **(C)** Progression-free survival evaluated using Response Evaluation Criteria in Solid Tumors version 1.1. (D) Time to prostate-specific antigen (PSA) progression. Tick marks indicate censored data. Analyses adjusted by age, bone lesions, PSA, and AKT values at baseline. SSE was not analysable with adjusted model; unadjusted data are presented.

Table 3
Adverse events possibly related to treatment.

Adverse events	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
Any, n (%)	26 (50.0%)	15 (28.8%)	8 (15.4%)	2 (3.8%)	1 (1.9%)
Hematologic					
Anaemia	3 (5.8%)	0	1 (1.9%)	1 (1.9%)	1 (1.9%)
Thrombocytopenia	3 (5.8%)	1 (1.9%)	0	2 (3.8%)	0
Leukopenia	1 (1.9%)	0	0	1 (1.9%)	0
Neutropenia	1 (1.9%)	0	1 (1.9%)	0	0
Non-haematologic					
Asthenia	13 (25.0%)	9 (17.3%)	4 (7.7%)	0	0
Diarrhoea	4 (7.7%)	2 (3.8%)	2 (3.8%)	0	0
Nausea	4 (7.7%)	4 (7.7%)	0	0	0
Anorexia	3 (5.8%)	3 (5.8%)	0	0	0
Arthralgia	3 (5.8%)	3 (5.8%)	0	0	0
Bone pain	3 (5.8%)	1 (1.9%)	2 (3.8%)	0	0
Fatigue	2 (3.8%)	1 (1.9%)	1 (1.9%)	0	0
Fever	2 (3.8%)	2 (3.8%)	0	0	0
Acute kidney injury	1 (1.9%)	0	1 (1.9%)	0	0
Burning	1 (1.9%)	1 (1.9%)	0	0	0
Dizziness	1 (1.9%)	1 (1.9%)	0	0	0
Epistaxis	1 (1.9%)	1 (1.9%)	0	0	0
Flank pain	1 (1.9%)	1 (1.9%)	0	0	0
Gastric discomfort	1 (1.9%)	1 (1.9%)	0	0	0
Pain	1 (1.9%)	0	1 (1.9%)	0	0
Vomiting	1 (1.9%)	1 (1.9%)	0	0	0

N: number of patients experiencing a specific AE treatment possibly related.
Health-related quality of life deteriorated between baseline and EoT, primarily in relation to patient physical (−3.6; 95%CI -5.8, −1.3; P = 0.005) and functional well-being (−3.0; 95%CI -5.3, −0.7; P = 0.016). Nevertheless, treatment with ^{223}Ra was overall considered safe and tolerable.

after progressing on first-line therapy. The most common AEs and premature discontinuations were in line with those reported in other studies treating patients with ^{223}Ra [9,21,22].

CTC count >5 at baseline has been associated with worse OS in mCRPC patients treated with ^{223}Ra [23], docetaxel [24], or abiraterone acetate [25]. In line with this, we found that patients whose CTC count decreased from ≥5 at baseline to <5 at EoT had a longer OS, suggesting that ^{223}Ra improves patient prognosis; however, the small sample size precluded establishing a definitive conclusion, and statistical significance was not reached.

AR-V7 in CTCs of patients with mCRPC has been associated with resistance to abiraterone acetate or enzalutamide and with worse prognosis [26–28]. Antonarakis *et al.* proved that, although AR-V7 status was not predictive of clinical resistance to taxanes, patients with AR-V7(+) mCRPC who were treated with taxanes showed a better outcome than AR-V7(+) patients treated with second-generation anti-androgen drugs abiraterone or enzalutamide [14,29]. Here, we investigated whether AR-V7 status would have a differential impact on enzalutamide- or abiraterone-treated men, and we observed that ^{223}Ra increases OS of patients with AR-V7(+) on CTCs compared to AR-V7(−). However, the low number of AR-V7(+) cases limited definitive conclusions on the utility of AR-V7 expression in patients who are treated with ^{223}Ra. Thus, these findings merit further investigations to evaluate the role of AR-V7 as a biomarker with predictive value for treatment with ^{223}Ra.

In the USA, most patients with mCRPC receive first- and second-line treatment with novel hormonal therapy [30,31]; nevertheless, therapy sequence differs in other countries [32–35]. For patients with mCRPC, cabazitaxel after docetaxel and novel hormonal therapy was found to achieve a longer median rPFS than that found in our study (8.0 versus 5.5 months, respectively); however, most of the patients in our study (92.3%) had not received docetaxel and, thus, cabazitaxel would not be an option for them [36]. Additionally, the advanced age of the patient population included in our study (median of 76.1 years) must be considered regarding its safety. ^{223}Ra can be a valuable treatment for patients with mCRPC and asymptomatic BMs who progress on novel hormonal therapy and who are ineligible for or refuse taxane-based therapy. Docetaxel achieved an rPFS of 9.0 months when given concurrently with ADT and 6.0 months when given as monotherapy to chemotherapy-naive patients with mCRPC and BMs [37]. However, retrospective studies showed a reduced clinical benefit from docetaxel following treatment with abiraterone, indicating a possible cross-resistance effect [38,39].

The pivotal ALSYMPCA trial with ^{223}Ra did not include patients with asymptomatic BMs [40]. Our study is the first to evaluate the role of ^{223}Ra specifically in this patient population. Moreover, a ^{223}Ra phase IIIb trial included asymptomatic and symptomatic patients, but only 40% and 8% of the treated patients had received prior abiraterone or enzalutamide, respectively [9]. Finally, these studies did not evaluate CTCs or AR-V7

expression. Of note, we observed a confirmed ALP response (according to ALP, biochemical response (≥30 and ≥ 50%) in our study was similar to that obtained in the ALSYMPCA trial (48.1% and 23.1% versus 47.1% and 27.4%, respectively).

Our findings show, for the first time, the clinical benefit of using ^{223}Ra for treating patients with mCRPC and asymptomatic BMs who have progressed on novel hormonal therapy and the role of AR-V7. Approved indications for ^{223}Ra vary from the USA or Australia that do have any limit to a specific line of treatment [41,42] to Europe restricting the ^{223}Ra indication to patients with mCRPC who have had two previous systemic treatments (other than ADT) or who cannot receive other treatments [43]. Although this recommendation was based on the results of the ERA 223 trial [11], many concerns have been raised about the potential missing opportunity to benefit from ^{223}Ra therapy for many patients with mCRPC who are more likely to have developed visceral disease [44]. We aim for our findings to establish the use of ^{223}Ra in the patient population considered here and to drive development of further studies.

One of the limitations of this study is the lack of baseline information of AR-V7 expression for 12 patients (23.1%). Another limitation is the small sample size, which precludes establishing an association between AR-V7 expression and survival. Nevertheless, AR-V7(+) patients had higher PSA values and more metastases, highlighting the prognostic value of AR-V7 status. Finally, the single-arm design prevents comparison of findings with patients who did not receive ^{223}Ra. However, this study also presents several strengths. First, the long follow-up time of up to 18 months for some patients allowed to adequately evaluate safety and tolerability of ^{223}Ra. Second, this is the first clinical trial using ^{223}Ra focused on patients with mCRPC and asymptomatic BMs, showing the role that AR-V7 plays in OS.

In conclusion, ^{223}Ra seems to be a reasonable treatment for patients with mCRPC and asymptomatic BMs who have progressed on abiraterone acetate or enzalutamide. AR-V7 expression in CTCs was significantly associated with OS but not with rPFS although, due to the limited sample size, these findings should be considered as hypothesis-generating and interpreted cautiously. Over the treatment course with ^{223}Ra, some patients experienced a reduction in CTC count and a switch in AR-V7 expression, which should be further explored in larger studies to assess their prognostic value.

Author contributions

Joan Carles, Miguel Sampayo-Cordero, and Andrea Malfettone had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Joan Carles.

Acquisition of data: Miguel Sampayo-Cordero.

Analysis and interpretation of data: All authors.

Drafting of the manuscript: All authors.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Miguel Sampayo-Cordero.

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Supervision: None.

Other: None.

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Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Bayer, Johnson & Johnson, Bristol-Myers Squibb, Astellas Pharma, Pfizer, Sanofi, MSD, Roche, AstraZeneca, Asofarma, Ipsen, AB Science, Aragon Pharmaceuticals, Arog Pharmaceuticals, Aveo Pharmaceuticals INC, Blueprint Medicines Corporation, BN Immunotherapeutics INC, Boehringer Ingelheim España, S.A., , Clovis Oncology INC, Cougar Biotechnology INC, Deciphera Pharmaceuticals LLC, Exelixis INC, F. Hoffmann-La Roche LTD, Genentech INC, GlaxoSmithKline, Incyte Corporation, -Cilag, International NV, Karyopharm Therapeutics INC., EISAI, Merck Serono, Lilly, Novartis Pharmaceutical, S.A, Janssen, Eusa Pharma, Sanofi-Genzyme, Beigene, VCN biotech, and VCN biotech; Leurquin Mediolanum SAS, Pierre Fabre, Rovi, Daiichi Sankyo, Techdow, Leo Pharma, Menarini, Ferrer, Millennium Pharmaceuticals, INC, Medimmune, Nanobiotix SA, S.L.U, Puma Biotechnology, FJ Pharma LTD. II, Teva Pharma S.L.U., MEDSIR.

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Appendix A. Supplementary data

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