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Efficacy of Radium-223 in Bone-metastatic Castration-resistant Prostate Cancer with and Without Homologous Repair Gene Defects

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Abstract

Background: Pathogenic mutations in genes mediating homologous recombination (HR) DNA repair are present in 20-30% of men with metastatic castrate-resistant prostate cancer (mCRPC). Radium-223 is a bone-seeking α-emitter that induces double-strand DNA breaks, thereby killing cancer cells in the bone microenvironment.

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Author contributions:

Emmanuel S. Antonarakis had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Antonarakis.

Acquisition of data: Velho, Qazi, Hassan.

Analysis and interpretation of data: Velho.

Drafting of the manuscript: Velho.

Critical revision of the manuscript for important intellectual content: Velho, Qazi, Hassan, Carducci, Denmeade, Markowski, Thorek, DeWeese, Song, Tran, Eisenberger, Antonarakis.

Statistical analysis: Velho.

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Supervision: Velho, Qazi, Hassan, Carducci, Denmeade, Markowski, Thorek, DeWeese, Song, Tran, Eisenberger, Antonarakis.

Other: None.

Objective: To evaluate the potential impact of germline or somatic HR-deficiency (HRD) mutations on radium-223 efficacy in bone mCRPC.

Design, setting, and participants: This is a retrospective single-institution study. Medical records of 190 mCRPC patients for whom germline and/or somatic DNA sequencing data were available were reviewed. Of these patients, 28 had received standard-of-care radium-223 at Johns Hopkins between February 2013 and February 2018.

Outcome measurements and statistical analysis: Alkaline phosphatase (ALP) responses and time-to-ALP-progression were the coprimary endpoints. Prostate-specific antigen (PSA) responses, overall survival (OS), and time to next systemic therapy were also evaluated.

Results and limitations: Of the 28 patients included, 10 men (35.7%) had a germline/somatic HRD mutation (three in *BRCA2,* and one each in *ATM, ATR, CHEK2, FANCG, FANCI, FANCL,* and *PALB2)* and 18 (64.3%) did not. Men with HRD mutations (HRD+) had numerically lower ages (66 vs 73 yr, $p = 0.25$), more soft-tissue metastases (50% vs 38%, $p = 0.43$), and higher baseline ALP levels (130 vs 108 U/l, $p = 0.84$). Compared with HRD(−) men, HRD(+) patients showed greater ALP responses (80% vs 38%, $p = 0.04$), longer time to ALP progression (median10.4 vs 5.8 mo, hazard ratio [HR] 6.4, $p = 0.005$), and a trend toward longer OS (median 36.9 vs 19.0 mo, HR 3.3, $p = 0.11$). PSA responses (0% vs 0%, $p > 0.99$) and time to next systemic therapy (HR 1.5, $p = 0.39$) were similar between the two groups. Results are limited by the retrospective nature of the analysis and the small sample size.

Conclusions: In this exploratory study, bone-metastatic mCRPC patients with inactivating HRD mutations demonstrated significantly improved ALP responses and time to ALP progression. These results should motivate prospective validation of the “synthetic lethality” hypothesis between HRD mutations and radium-223 activity.

Patient summary:

In this report, we retrospectively examined outcomes to metastatic prostate cancer in patients with and without DNA repair mutations who received radium-223, a therapy that kills cancer cells by causing direct DNA damage. Our study suggested that patients who have inherited or acquired DNA repair gene mutations derived greater benefit from radium-223 when compared with patients without these mutations. We concluded that radium-223 might have an important role in this setting; however, prospective studies are needed to confirm whether DNA repair mutations truly make radium-223 work better or not.

Keywords

Cancer; DNA repair; Germline; Mutations; Prostate cancer; Radium-223; Somatic

1. Introduction

Prostate cancer (PCa) is a heterogeneous disease at the clinical, pathological, and molecular levels. Based on genetic abnormalities, especially in genes that control mechanisms of DNA repair, new attempts to classify the different molecular subgroups of this disease have been made [1]. In recent years, the critical importance of DNA repair defects, especially in the homologous recombination (HR) pathway as well as the mismatch repair pathway, has been

demonstrated in both germline and somatic lineages, and has prognostic and therapeutic implications [1,2]. The genes responsible for the HR pathway, particularly *BRCA1, BRCA2, CHEK2, ATM, RAD51D,* and *PALB2,* play a crucial role in repairing double-strand (ds) DNA breaks [3]. Defects in some of these genes have been associated with an increased risk of PCa development and disease aggressiveness [4,5].

Germline mutations in DNA repair genes are present in 8-12% of metastatic PCa [1,2], whereas the previously estimated prevalence was 4-5% in localized disease [6,7]. In addition, somatic aberrations in genes responsible for DNA repair are seen in 20-25% of PCa patients [1]. Different studies have confirmed that together both germline and somatic HR-deficiency (HRD) pathogenic mutations are seen in up to one-third of patients with metastatic castration- resistant prostate cancer (mCRPC) [1,8], strengthening not only the high prevalence of these mutations but also their role as prognostic [9-12] and predictive biomarkers [8,13].

Radium-223 is an alpha-particle-emitting bone-targeted therapy that demonstrated consistent improvement in pain [14,15] and overall survival (OS) in patients with mCRPC harboring bone disease [16]. Alpha particles emitted at the site of disease have high linear energy transfer, resulting in the deposition of energy in the immediate vicinity of the radionuclide's decay. This highly localized radiotherapy selectively targets the bone microenvironment and metastatic tumor cells, causing unrepairable dsDNA breaks [17], resulting in potent but locally restricted cytotoxic effects [18]. By the mechanism of synthetic lethality, tumors with defects in mechanisms of DNA repair are theoretically more susceptible to therapies that cause DNA damage, such as ds breaks [19,20]. Therefore, the present study hypothesized that patients who harbor germline and/or somatic HRD mutations may have a greater clinical benefit from radium-223, due to dsDNA breaks going unrepaired because of an underlying HRD in the tumor cells [21]. To this end, we performed a retrospective study to test this biological hypothesis.

2. Patients and methods

Patients with mCRPC who received radium-223 over a 5-yr period (between February 2013 and February 2018) and who were being seen at the Johns Hopkins Hospital formed the study population. These consecutive patients were offered somatic and/or germline genomic panel testing for clinical purposes, using different commercially available (Foundation One, Personal Genome Diagnostics, Color Genomics, Invitae) and in-house next-generation DNA sequencing platforms. This was an unselected patient cohort; patients were not selected for radium-223 treatment based on prior knowledge of HRD mutation status. The Johns Hopkins University Institutional Review Board and the Human Research Ethics Committee approved this retrospective study.

Demographic, histopathological, and clinical characteristics of all patients were collected. We interrogated for the presence or absence of pathogenic or likely pathogenic somatic and/or germline HRD mutations, and classified patients into mutation-positive (HRD+) and mutation-negative (HRD-) groups. The coprimary clinical endpoints were alkaline phosphatase (ALP) response (defined as a decline of ≥30% from baseline within 12 wk) and

time to ALP progression (defined as an increase in ALP level of ≥25% from baseline in patients with no decrease from baseline or an increase of ≥25% above the nadir in patients with an initial decrease from baseline). Prostate-specific antigen (PSA) response rate (a decline of ≥50% from baseline within 12 wk), OS, and time to next systemic therapy were also assessed. In order for patients to be evaluable for ALP response rates and PSA response rates, a minimum of 12 wk of ALP/PSA data were required following initiation of radium-223 treatment (all patients met this criterion for both parameters).

The sample size was opportunistically selected (based on cross referencing of our clinical genomics database and our radium-223 pharmacy database) and was not based on prospective hypothesis testing. A two-sided Fisher's exact test was used to compare proportions for categorical baseline variables (eg, Gleason score, baseline Eastern Cooperative Oncology Group [ECOG] status, proportion of patients with visceral or soft tissue disease, and proportion of patients who received a previous taxane) between HRD+ and HRD- patients. The Mann-Whitney *U* test was used to compare distributions of age, number of radium-223 doses received, baseline pain score, and PSA and ALP between the two groups. All statistical tests were two sided, with statistical significance set at $p \leq 0.05$. Since this study was hypothesis generating, we did not perform Bonferroni corrections for multiple comparisons. Kaplan-Meier curves were used to visualize time-to-event data. Hazard ratios, associated 95% confidence intervals (CIs), and differences between groups were calculated with the use of a Cox proportional-hazards model.

3. Results

3.1 Baseline genomic and clinical characteristics

Between February 15, 2013 and February 15, 2018, a total of 190 mCRPC patients agreed to undergo clinical-grade somatic and/or germline genetic testing using the next-generation DNA sequencing platforms listed above. All germline testing was performed from saliva. Somatic testing involved a mix of primary tumor testing as well as from metastatic biopsies. Of these 190 mCRPC cases, 28 patients had received radium-223 at some point during their treatment course, forming our study population. No patients had received either PARP inhibitors or platinum agents prior to radium. Among these 28 men, pathogenic or likely pathogenic HRD mutations were identified in 10 patients (36%), while 18 men (64%) did not harbor any HRD mutations. Pathogenic alterations were defined a priori as those that resulted in protein- truncating defects (nonsense mutations, frameshift insertions or deletions, and splice site mutations at the conserved splice donor and acceptor sites) or missense mutations that were denoted as pathogenic in the ClinVar database. The HR genes of interest included in this study were *BAP1, BARD1, BRAP, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, GEN1, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D,* and *RAD54L;* this list of 25 genes was also specified a priori. Table 1 summarizes the 10 pathogenic HRD mutations found in these patients. A complete list of mutations, including those in genes other than DNA repair genes, is listed in Supplementary Table 1.

Demographic, clinical, and pathological characteristics of our patients are shown in Table 2. Despite some numeric differences between HRD+ and HRD- patients, no statistically

significant differences were seen between the two groups. Patients with deleterious HRD mutations had a trend toward younger ages at the time of radium-223 use (66 vs 73 yr, $p = 0.25$), higher Gleason sums (Gleason ≥8 in 80% vs 66%, $p = 0.44$), more visceral and soft tissue disease (50% vs 38%, $p = 0.43$), and higher baseline ALP levels (130 vs 108 U/l, $p = 0.84$). All patients had an ECOG score of 0-1 when they started radium-223 treatment, and there was no difference in the number of cycles of the drug between the two groups (five vs five cycles, $p > 0.99$).

3.2 Efficacy of radium-223 in patients with and without HRD mutations

Overall, 53% (15/28) of all patients had a decline of ≥30% in ALP within 12 wk, meeting the cutoff for an ALP response. Patients with an HRD mutation (HRD+ men) had a statistically significant improvement in ALP response rates compared with HRD- patients (80% vs 38%, $p = 0.04$; Table 3). Despite some marginal reductions in PSA levels seen in 18% (5/28) of all patients, no individual had a PSA decline of ≥50% from baseline within 12 wk. The relationship between ALP response and PSA response according to HRD status is depicted in the waterfall plots in Figures 1 and 2, respectively. In addition, of those individuals who had elevated ALP levels at baseline, all patients with HRD mutations (five of five patients) had normalization of ALP after starting radium-223 compared with only one-third (three of nine patients) of HRD- patients (100% vs 33%, $p = 0.03$; Table 3).

All the primary and secondary endpoints favored patients with HRD mutations, although not all associations were statistically significant. Compared with HRD- patients, HRD+ men had significantly prolonged time to ALP progression (median 10.4 vs. 5.8 mo; hazard ratio [HR] 6.4, 95% CI, 1.5-28.9; $p = 0.005$; Fig. 3). Time to the next systemic therapy was also numerically longer in HRD+ compared with HRD- patients (median 9.7 vs 7.2 mo; HR 1.5, 95% CI, 0.5-5.3; $p = 0.39$; Fig. 4). Finally, median OS was 36.9 versus 19.0 mo in patients with versus without HRD mutations (HR 3.3, 95% CI, 0.7-15.6; $p = 0.11$; Fig. 5).

4. Discussion

The findings of our hypothesis-generating study support the theoretical rationale that tumors harboring HRD mutations may be more sensitive to therapies that cause direct damage to DNA, such as radium-223. In the pivotal phase III ALSYMPCA study [16], which compared radium-223 versus placebo plus best supportive care, ALP response rates (≥30% declines from baseline) were found in 47% versus 3% of patients ($p < 0.001$). In our study, the overall ALP response rate in the unselected population broadly mirrored this estimate, but the ALP response rate was considerably higher in patients with HRD mutations (80% vs 38%, $p = 0.04$); there was also a difference in the proportion of patients who normalized their ALP level with radium-223 treatment depending on HRD status (100% vs 33%, $p = 0.03$). Furthermore, the median time to ALP progression in our study was significantly longer in HRD+ patients (10.4 vs 5.8 mo, $p = 0.005$) compared with HRD- patients. This time to delay of ALP progression in the HRD+ group also appears to be greater than that in the pivotal phase III trial (which showed 7.4 vs 3.8 mo until ALP progression for radium-223 and placebo, respectively) [16], although direct comparisons cannot be made.

Finally, HRD+ patients had numerically longer OS compared with HRD- men, although this analysis was clearly underpowered to demonstrate a statistical improvement.

Our study primarily used ALP endpoints to evaluate the hypothesis that patients with HRD might have a greater benefit from radium-223 than those with HR-proficient tumors. Why was such an emphasis placed on ALP-based endpoint? This is because there are data indicating that within patients with mCRPC and bone metastasis who receive chemotherapy, serum ALP responses may be prognostic for OS independently of PSA changes [22]. In addition, in an exploratory analysis of the ALSYMPCA trial [23], it was demonstrated that patients with ≥30% ALP declines had a 55% relative reduction in the risk of death compared with patients who did not have ALP declines [23]. Finally, focusing on ALP-related endpoints seemed to be reasonable in the context of a bone-targeting therapy. Taken together, these data suggest that improvements in ALP response rates and prolongation of ALP progression (as found in the HRD+ men in our study) are reasonable intermediate endpoints to evaluate the clinical efficacy of radium-223.

Despite some recent case reports [24] and a case series [25] suggesting favorable responses to radium-223 in patients with HRD mutations, our study is the first (to our knowledge) that includes a control group of HRD- patients undergoing radium-223 treatment. Thus, this enabled us to compare outcomes in HRD+ versus HRD- men. Multiple recent studies have tried to assess the impact of DNA repair mutation status on response or resistance to standard-of-care therapies, with conflicting results. Some studies, for example, show no clear difference in prognosis according to HRD status with respect to taxane chemotherapies or novel AR-targeting therapies [26]. With respect to abiraterone and enzalutamide efficacy specifically, some studies have demonstrated a worse prognosis in men with HRD mutations [27], while others have suggested improved outcomes in the HR-deficient subsets [28]. However, the theoretical rationale for why an HR-deficient patient should respond better or worse to an AR- targeted therapy or a taxane chemotherapy appears weaker than that supporting the biological concept that an underlying HRD may produce a form of “synthetic lethality” in the setting of an alpha-particle-emitting dsDNA break-inducing agent.

If validated, our study results may impact clinical decisions, and aid therapy selection for radium-223 treatment and the evaluation of experimental alpha-particle emitters. With the wide availability of clinical-grade next-generation DNA sequencing panels, mutational profiles of many cancers (as well as their inherited backgrounds) are now increasingly being recognized. Notably, the recent National Comprehensive Cancer Network 2018 PCa guidelines [29] now recommend germline DNA testing for all men diagnosed with mCRPC, the same population in which radium-223 is indicated. Since multiple treatment options may be available to patients with bone-predominant mCRPC, knowing that a patient has a germline and/or somatic HRD mutation might make a clinician reach sooner for radium-223 in this context, perhaps saving other systemic therapies (eg, taxane chemotherapies) for later. Clearly, prospective validation of these hypothesis-generating results will be required before these findings become clinically actionable. Finally, these data may ignite interest in conducting dedicated clinical trials evaluating the use of radium-223 in biomarker-selected (ie, HR-deficient) mCRPC populations.

Our study has several limitations that should be considered when interpreting our results. First, this was a retrospective study and the sample size was not determined a priori using hypothesis testing; therefore, even though some strong associations may have been demonstrated, causal inferences cannot be made. Other inherent limitations of this retrospective study design include selection bias and information bias. We tried to mitigate selection bias by including consecutive patients who received radium-223 and had next-generation DNA sequencing data available. However, despite our study having a limited number of patients (which might cause limitations in the analysis, especially because of wide confidence intervals and nonsignificant *p* values), the study still met its primary endpoint, which was to demonstrate a greater benefit of radium-223 with respect to ALP endpoints in patients with HRD mutations. In particular, care should be taken when interpreting the Kaplan-Meier curves due to the very small number of patients per group (18 and 10 patients in the HRD- and HRD+ groups, respectively), resulting in very wide confidence intervals. Finally, due to the small sample size and the hypothesis-generating nature of this study, we were unable to control for potential discrepancies in baseline clinical factors. These results would now benefit from further prospective (or retrospective) validation, and must be considered hypothesis generating only and not definitive.

5. Conclusions

Our preliminary findings suggest that bone-metastatic mCRPC patients with germline and/or somatic mutations in HR-pathway genes may be associated with clinical benefit from radium- 223 (in terms of ALP responses, normalization of ALP, and the time to ALP progression) as well as potential prolongation of survival. The retrospective nature of our study and the limitations inherent to that design suggest that these provocative findings should be considered as hypothesis generating only at this time, but may spark dedicated trials investigating radium-223 in HR-deficient mCRPC patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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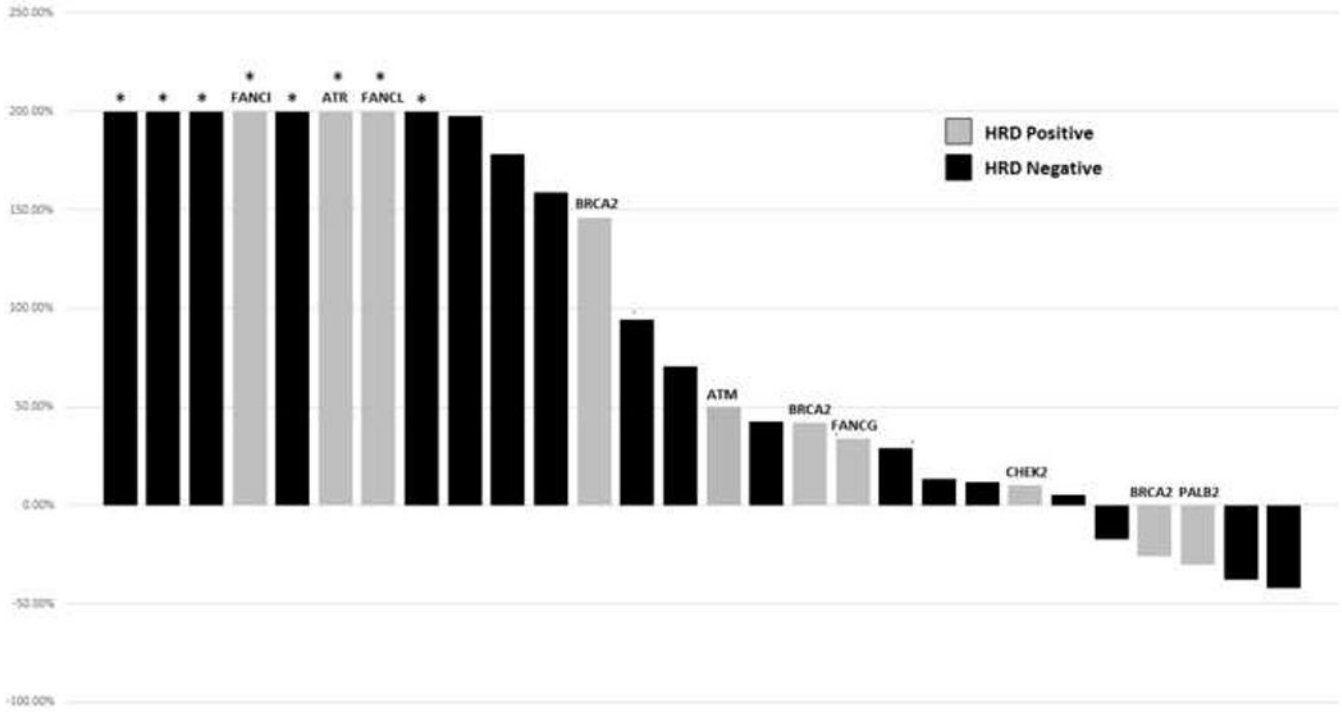

Fig. 1 –.

Waterfall plot of best PSA response within 12 wk, by HRD status. HRD = homologous recombination deficiency; PSA = prostate-specific antigen. * Indicates truncated bars at > +200%.

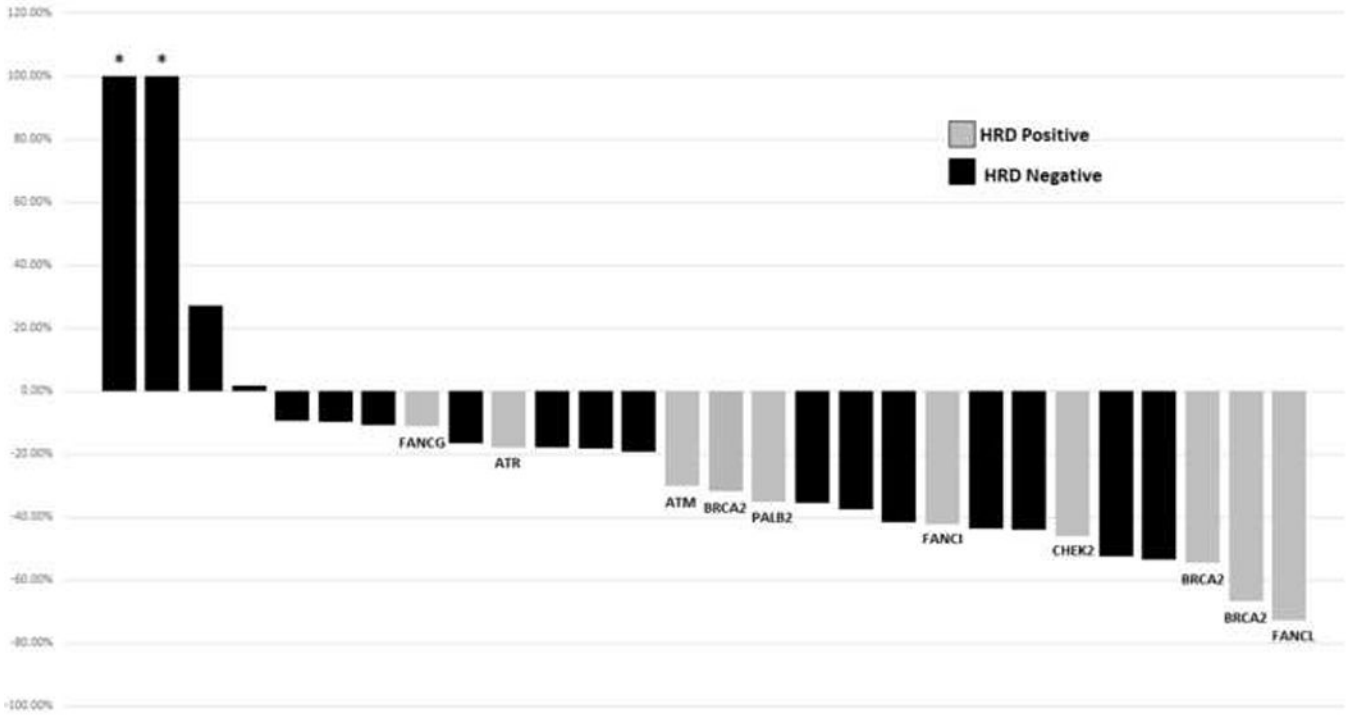

Fig. 2 –.

Waterfall plot of best alkaline phosphatase response within 12 wk, by HRD status. HRD = homologous recombination deficiency; PSA = prostate-specific antigen. * Indicates truncated bars at >+100%.

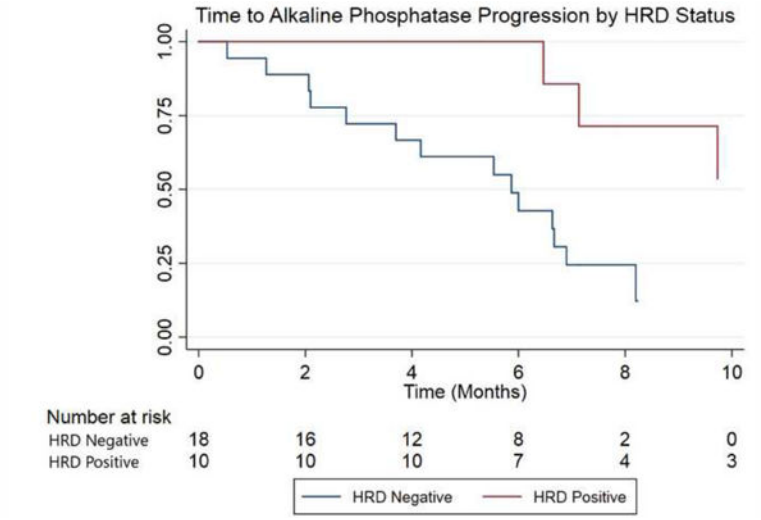

Fig. 3 –.

Kaplan-Meier curve for time to ALP progression, by HRD status (the *x*-axis is truncated at 10 mo). ALP = alkaline phosphatase; HRD = homologous recombination deficiency.

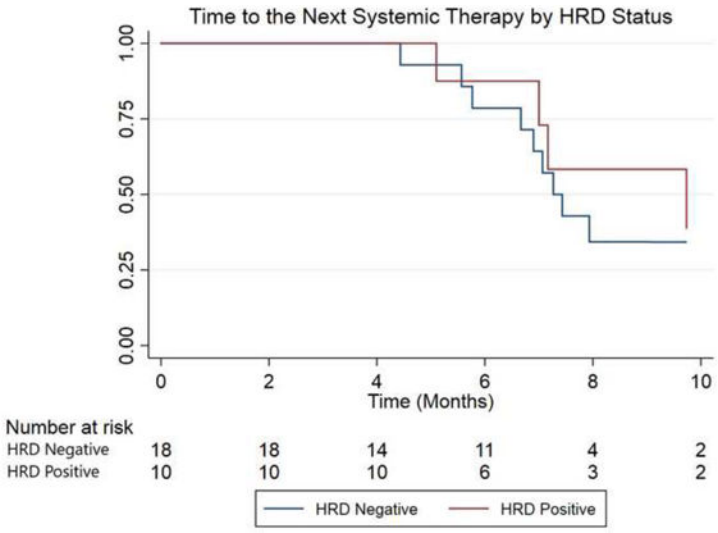

Fig. 4 –.

Kaplan-Meier curve for time to the next systemic therapy, by HRD status (the *x*-axis is truncated at 10 mo). HRD = homologous recombination deficiency.

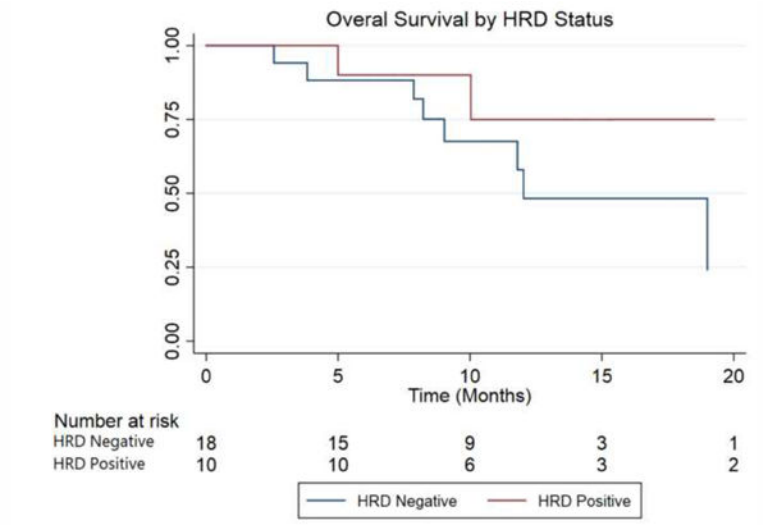

Fig. 5 –.

Kaplan-Meier curve for overall survival, by HRD status (the *x*-axis is truncated at 20 mo). HRD = homologous recombination deficiency.

Table 1 –

List of pathogenic homologous recombination deficiency (HRD) mutations

Sample ID	Gene	Origin of mutation	Amino acid change	Nucleotide change	Mutation mechanism	Type of analysis
02	*BRCA2*	Germline	D3095E	c.9285C>G	Missense	Germline + somatic
03	*BRCA2*	Somatic	E1646Qfs*23	c.4936_4939delGAAA	Frameshift deletion	Germline + somatic
14	*CHEK2*	Somatic	R519X*	c.1555C>T	Nonsense	Germline + somatic
15	*ATM*	Somatic	E2014X*	c.6040G>T	Nonsense	Germline + somatic
18	*ATR*	Germline	-	c.2634-1G>A	Splicing	Germline only
19	*FANCI*	Germline	K808X*	c.A2422T	Nonsense	Germline only
20	*FANCL*	Somatic	T372Nfs*4	c.A2422T	Frameshift insertion	Germline + somatic
29	*PALB2*	Somatic	-	c.212-2A>G	Splicing	Germline + somatic
31	*FANCG*	Germline	L53Afs*4	c.156insG	Frameshift insertion	Germline + somatic
32	*BRCA2*	Somatic	S3147Cfs*2	c.9435_9436delGT	Frameshift deletion	Germline + somatic

Table 2 –

Baseline demographic, clinical, and pathological characteristics of our patient cohort, according to HRD status

	Patient characteristics		
	HRD(+) (*N* = 10)	**HRD(-) (*N* = 18)**	***p* value**
Median age in years (Q1-Q3)	66 (60-69)	73 (64-75)	0.28
Number of radium-223 doses received	5.5	5.5	0.50
Median number (Q1-Q3)	(5-6)	(2-6)	
Gleason sum at diagnosis, % (*N*)			
≤7	10 (1)	33 (6)	
≥8	80 (8)	67 (12)	0.44
Not reported	10 (1)	0 (0)	
ECOG status at time of radium-223			
0-1	100% (10)	100% (18)	>0.00
≥2	0% (0)	0% (0)	
Bone pain score at time of radium-223	2	1	0.58
Median (Q1-Q3)	(0-3)	(0-2.5)	
Presence of any soft-tissue disease at time of radium-223	50% (5)	39% (7)	0.43
Previous taxane use	50% (5)	44% (8)	0.54
Baseline PSA level (ng/ml)	77.1	71.6	1.00
Median (Q1-Q3)	(7.9-236.0)	(18.4-162.9)	
Baseline alkaline phosphatase (U/l)	130	108.5	0.70
Median (Q1-Q3)	(85-194)	(72-185)	

ECOG = Eastern Cooperative Oncology Group; HRD = homologous recombination deficiency; PSA = prostate-specific antigen.

[a]Tests used were the two-sided Fisher's exact test and Mann-Whitney test.

Table 3 –

PSA and ALP responses in HRD(+) and HRD(-) patients

	HRD(+)	HRD(-)	*p* value
	***N* = 10**	***N* = 18**	
PSA (≥50%) response	0% (0)	0% (0)	1.00
ALP (≥30%) response	80% (8)	39% (7)	0.04
Patients with ALP normalization (if baseline ALP was elevated)	100% (5)	33% (3)	0.03

ALP = alkaline phosphatase; HRD = homologous recombination deficiency; PSA = prostate-specific antigen.

[a]Response rate is defined as a decrease in PSA of ≥50% and in ALP of ≥30% from baseline within 12 wk.