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Original Article

Impact of homologous recombination repair/BReast CAncer (*BRCA*) gene alterations on survival in a real-world setting of metastatic prostate cancer

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Objective

To investigate alterations of homologous recombination repair (HRR) and especially BReast CAncer 1/2 (*BRCA*1/2) gene on overall survival (OS). Moreover, to explore the effect of inhibition of poly(ADP-ribose)-polymerase (PARPi) as systemic therapy for metastatic castration-resistant prostate cancer (mCRPC).

Patients and methods

Of all HRR-screened patients with metastatic prostate cancer, baseline characteristics were sampled. Kaplan–Meier estimates and multivariable Cox regression models predicted the effect of HRR/*BRCA*1/2 alterations on OS.

Results

Of 196 eligible patients, 61 (31%) harboured any HRR and 40 (20%) *BRCA*1/2 alterations. Of HRR alterations, 40 (66%) vs six (10%) vs five (8.2%) vs four (6.6%) vs two (3.3%) vs four (6.6%) were *BRCA*1/2 vs Ataxia-telangiectasia mutated kinase (*ATM*) vs checkpoint kinase 2 (*CHEK*2) vs cyclin-dependent kinase 12 (*CDK*12) vs Fanconi anaemia complementation Group A (*FANCA*) vs positive for other mutations. Of these, 30% received a PARPi. OS differed significantly between HRR-positive vs -negative patients. Specifically in hormone-sensitive prostate cancer, the median OS was 63 (HRR positive) vs 57 (*BRCA*1/2 positive) vs 113 months (HRR negative) ($P \leq 0.01$). In mCRPC, OS was 42 (HRR positive) vs 41 (*BRCA*1/2 positive) vs 70 months (HRR negative) ($P \leq 0.01$). HRR and *BRCA*1/2 alterations were associated with worse OS after multivariable adjustment. Finally, patients with mCRPC with *BRCA*1/2 mutation treated without PARPi harboured worse OS than patients with *BRCA*1/2 mutation and PARPi therapy (median OS: 33 vs 48 months, $P < 0.03$).

Conclusion

Incidence of HRR alteration in a clinical real-world setting is high when using blood- and tissue-based tests. Patients with HRR/*BRCA* alterations have worse outcomes resulting in significant OS differences between HRR/*BRCA*-positive patients with mCRPC with and without PARPi usage vs HRR/*BRCA*-negative patients.

Keywords

metastatic prostate cancer, mutation, metastatic hormone-sensitive prostate cancer, mutation, BReast CAncer (*BRCA*) gene

Introduction

The management of metastatic hormone-sensitive prostate cancer (mHSPC) and castration-resistant prostate cancer (mCRPC) has undergone significant transformations in recent years and remains a subject of ongoing research to identify optimal treatment modalities and sequences [1–3]. Over this period, there has been a shift from using androgen-deprivation therapy alone as the standard of care for all patients with mHSPC and mCRPC to incorporating a combination of new androgen receptor signalling inhibitor (ARSI), chemotherapy, or a combination of both, contingent

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upon tumour attributes like metastatic burden [4–6]. Moreover, for mCRPC, inhibitors of poly(ADP-ribose)-polymerase (PARPi) are approved as monotherapy or in combination with ARSI and currently ongoing trials test for its effect in mHSPC [7–11]. The PARPi approval is mainly based on extended radiographic progression-free survival of the prospective phase III trials PROfound (olaparib monotherapy; ClinicalTrials.gov identifier [ID] NCT02987543), PROpel (olaparib + abiraterone; ClinicalTrials.gov ID NCT03732820), TALAPRO-2 (talazoparib + enzalutamide; ClinicalTrials.gov ID NCT03395197) and MAGNITUDE (niraparib + abiraterone; ClinicalTrials.gov ID NCT03748641). Best response rates in these phase III trials were observed in patients with mCRPC with mutations in BReast CAncer 1/2 (*BRCA*1/2) genes or alterations in homologous recombination repair genes (HRR).

As molecular testing for these genetic alterations becomes increasingly crucial, there is a growing scientific focus on practical guidelines and testing pathways, as well as sequential therapies for HRR-positive or *BRCA*-positive patients with mCRPC [12,13]. However, only a few studies have addressed the effect of real-world application of PARPi and its influence on overall survival (OS) in mCRPC [14].

We addressed this void and relied on our institutional metastatic prostate cancer database to unravel real-world evidence regarding incidence of HRR and *BRCA* alternations and the administration of PARPi in a clinical setting. We hypothesised that patient and tumour characteristics, as well as OS differs significantly between HRR-positive and *BRCA*-positive patients, relative to negative tested patients with metastatic prostate cancer. Moreover, we hypothesised that the usage of PARPi in *BRCA*-positive patients prolongs survival.

Patients and Methods

Study Population

Following the endorsement of the local ethics committee (identifier: SUG-5-2018) and adherence to the principles outlined in the Declaration of Helsinki, we retrospectively identified all patients with metastatic prostate cancer at the Department of Urology, University Hospital Frankfurt, Germany since 2018 (n = 561). Inclusion criteria were restricted to patients with metastatic prostate cancer who underwent any testing for HRR or *BRCA* alterations. These criteria resulted in the identification of 196 eligible patients with mHSPC or mCRPC.

The HRR and *BRCA* Alterations

Information regarding alterations in HRR and *BRCA* genes were sampled from patients' files and were considered positive if prostate cancer tissue, metastatic tumour tissue and/or a liquid biopsy yielded a positive test result (defined as positive in clinical setting by Uropathologists and Urologists). If *BRCA* tested positive similar to other HRR alterations, it was categorised as '*BRCA* positive'. In this real-world scenario, for tissue testing different tests with different gene panels were used. Patients with a negative or failed test or insufficient test reports were grouped as 'HRR/*BRCA* negative'. HRR and *BRCA* alterations were grouped as positive irrespective of the time point of testing during metastatic prostate cancer treatment in the clinical setting. The patient could have more than one test result and both, liquid biopsy and tumour tissue testing.

Statistical Analysis

Descriptive statistics comprised frequencies and proportions for categorical variables. Medians and interquartile ranges (IQRs) were provided for all continuously coded variables. The chi-square test was utilised to assess the statistical significance of differences in proportions, while the t-test and Kruskal–Wallis test were employed to examine differences in distributions.

Two distinct sets of analyses were conducted: First, comparisons between HRR-positive and -negative patients, as well as between *BRCA*-positive and -negative patients. Additionally, the utilisation of PARPi was factored into sensitivity analyses for OS. Kaplan–Meier curve-based estimates, along with uni- and multivariable Cox regression models were employed for all OS analyses. Multivariable adjustment was carried out for variables that remained significant in the univariable regression models.

All tests were two-tailed with a significance level set at $P < 0.05$. The R software environment for statistical computing and graphics (version 3.4.3; R Foundation for Statistical Computing, Vienna, Austria) was utilised for all analyses.

Results

Baseline and Tumour Characteristics

Of 196 HRR-screened patients with metastatic prostate cancer, 61 (31%) harboured any HRR-positive alteration (Table 1). The median (IQR) follow-up was 43 (26–63) months. The median (IQR) age of all included patients was 66 (59–72) years and did not differ between HRR-positive and -negative patients (P = 0.2). Similarly, the median PSA level at diagnosis of metastatic prostate cancer, PSA nadir during mHSPC treatment and PSA at progression of mCRPC did not differ between both groups (all $P \geq 0.3$). Conversely, HRR-positive patients exhibited significantly higher proportion of primary metastatic prostate cancer disease than their HRR-negative counterparts (79% vs 64%, P = 0.039). Moreover, proportion of high-volume (69% vs 56%) and

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Table 1 Descriptive baseline and tumour characteristics of 196 patients screened for HRR alterations, stratified according to HRR-negative vs -positive.

Variable	Overall, *n* = 196	HRR negative, *n* = 135 (69%)	HRR positive, *n* = 61 (31%)	*P*
Age at mPCa, years, median (IQR)	66 (59–72)	66 (59–72)	64 (59–70)	0.2
PSA level at mPCa, ng/mL, median (IQR)	82 (16–276)	90 (13–270)	77 (18–334)	0.9
PSA nadir mHSPC, ng/mL, median (IQR)	0.4 (0.05–2.7)	0.6 (0.07–2.9)	0.3 (0.04–0.9)	0.3
PSA level at mCRPC, ng/mL, median (IQR)	13 (3–54)	12 (3–47)	18 (4–63)	0.7
Therapy lines for mPCa, *n*, median (IQR)	4 (2–5)	3 (2–5)	4 (2–5)	0.5
ECOG PS status ≥2, *n* (%)	3 (2.5)	1 (1.4)	2 (4.2)	0.6
Gleason Score 8–10, *n* (%)	134 (73)	87 (70)	47 (80)	0.2
Local therapy (RP/RT), *n* (%)	79 (40)	54 (40)	25 (41)	0.9
Primary mPCa, *n* (%)	129 (69)	81 (64)	48 (79)	0.039
Primary visceral metastatis, *n* (%)	17 (9.7)	10 (8.4)	7 (13.0)	0.4
High-volume mHSPC, *n* (%)	79 (60)	48 (56)	31 (69)	0.15
High-risk mHSPC, *n* (%)	88 (65)	56 (63)	32 (68)	0.5

Abbreviations: ECOG PS, Eastern Cooperation Oncology Group Performance Status; mPCa, metastatic prostate cancer; RP, radical prostatectomy; RT, radiation therapy.

high-risk disease (68% vs 63%) and Gleason Score 8–10 (80% vs 70%) were higher in the HRR-positive group, despite not reaching statistical significance (all $P \geq 0.15$). Proportions of local therapy to the prostate did not differ between both groups (41% vs 40%, $P = 0.9$).

Treatment with PARPi and HRR Alterations

Overall, 107 (55%) patients were HRR tested in tissue only, 19 (9.7%) in a liquid biopsy only, and 70 (36%) patients in both. Of 61 clinically positive HRR-screened patients with metastatic prostate cancer, 40 (66%) vs six (10%) vs five (8.2%) vs four (6.6%) vs two (3.3%) vs four (6.6%) were positive for *BRCA*1/2 vs Ataxia-telangiectasia mutated kinase (*ATM*) vs checkpoint kinase 2 (*CHEK*2) vs cyclin-dependent kinase 12 (*CDK*12) vs Fanconi anaemia complementation Group A (*FANCA*) vs positive for other mutations, respectively (Table 2). Of HRR-positive patients, 18 (30%) received PARPi treatment compared to six (4.4%) of the patients without HRR alterations. Of all *BRCA*-positive patients, 14 (34%) received a PARPi. PARPi treatment was mostly administered in the second, third and fourth line of mCRPC treatment (each six patients) and in nine patients together with ARSI (50%). Detailed treatment characteristics for each group are shown in Table 2.

Time to mCRPC

Comparing the time to mCRPC, there were no differences between HRR-negative vs -positive patients (Fig. S1A, median

Table 2 Gene alternation and treatment characteristics of 196 patients screened for HRR alterations, stratified according to HRR-negative vs -positive.

Variable, *n* (%)	Overall, *n* = 196	HRR negative, *n* = 135 (69%)	HRR positive, *n* = 61 (31%)	*P*
HRR alteration				
*BRCA*1/2	40 (20)		40 (66)	
ATM	6 (3.1)		6 (10)	
CDK12	4 (2.0)		4 (6.6)	
CHEK2	5 (2.6)		5 (8.2)	
FANCA	2 (1.0)		2 (3.3)	
Other	4 (2.0)		4 (6.6)	
PARPi treatment	24 (12)	6 (4.4)	18 (30)	<0.001
Treatment of mHSPC				
ADT monotherapy	8 (6.7)	8 (10)	0 (0)	0.2
ARSI	65 (54)	41 (51)	24 (60)	
Docetaxel	36 (30)	25 (31)	11 (28)	
Triplet therapy	6 (5.0)	4 (5.0)	2 (5.0)	
Other	5 (4.2)	2 (2.5)	3 (7.5)	
First-line treatment in mCRPC				
ADT monotherapy	6 (3.1)	6 (4.4)	0 (0)	0.10
Chemotherapy	45 (23)	30 (22)	15 (25)	
Lu-PSMA	3 (1.5)	2 (1.5)	1 (1.6)	
ARSI	100 (51)	72 (53)	28 (46)	
PARPi ± ARSI	6 (3.1)	1 (0.7)	5 (8.2)	
Radium	2 (1.0)	2 (1.5)	0 (0)	
None/Other/NA	40 (20)	25 (19)	15 (25)	

Abbreviations: ADT, androgen-deprivation therapy; Lu-PSMA, lutetium-177-prostate-specific membrane antigen; NA, unknown.

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time: 17.0 vs 16.8 months, $P = 0.6$), as well as *BRCA*-negative vs -positive mHSPC (Fig. S1B, median time: 17.0 vs 16.8 months, $P = 0.5$).

Survival of HRR and *BRCA* Positive Patients with mHSPC

Comparing the OS of HRR-negative vs -positive patients with mHSPC (Fig. 1A), there was a significant median OS difference of 113 vs 63 months, resulting in a hazard ratio (HR) of 1.88 ($P = 0.02$). In multivariable Cox regression models controlling for unfavourable patient and tumour characteristics, HRR-positive status was no longer a predictor of worse OS (HR 1.16, $P = 0.7$).

Comparing the OS of *BRCA*-negative vs -positive patients with mHSPC (Fig. 1B), there was also a significant median OS difference (113 vs 57 months), resulting in a HR of 2.01 ($P = 0.015$) for *BRCA*-positive patients. In multivariable Cox regression models, *BRCA* alterations were not independently associated with worse OS in patients with mHSPC (HR 1.05, $P = 0.9$).

Influence of HRR and *BRCA* Alterations in Patients with mCRPC

After progression to mCRPC, the median OS for HRR-negative vs -positive patients was 70 vs 42 months (Fig. 2A), resulting in a HR of 2.20 ($P < 0.01$). Moreover, after controlling for patient and tumour characteristics in multivariable Cox regression models, HRR alteration was an independent predictor of worse OS for patients with mCRPC (HR 1.97, $P = 0.044$).

Comparing *BRCA*-positive vs -negative patients with mCRPC, the median OS was 70 vs 41 months (Fig. 2B), resulting in a

Fig. 1 The OS in mHSPC comparing (**A**) HRR-positive (pos.) vs -negative (neg.) and (**B**) *BRCA*1/2-pos. vs -neg. patients.

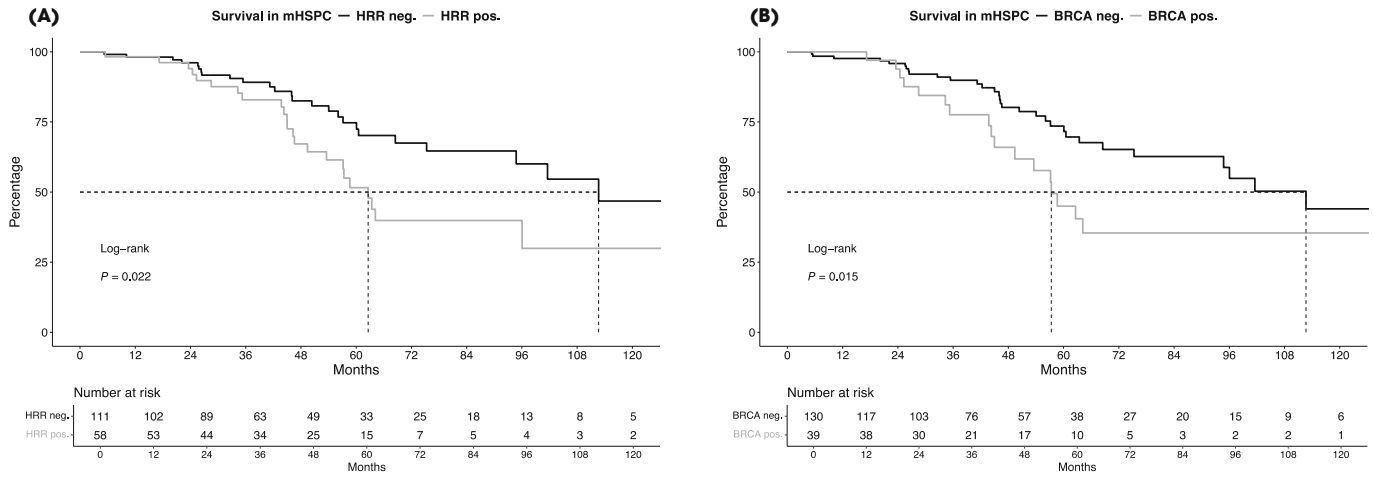
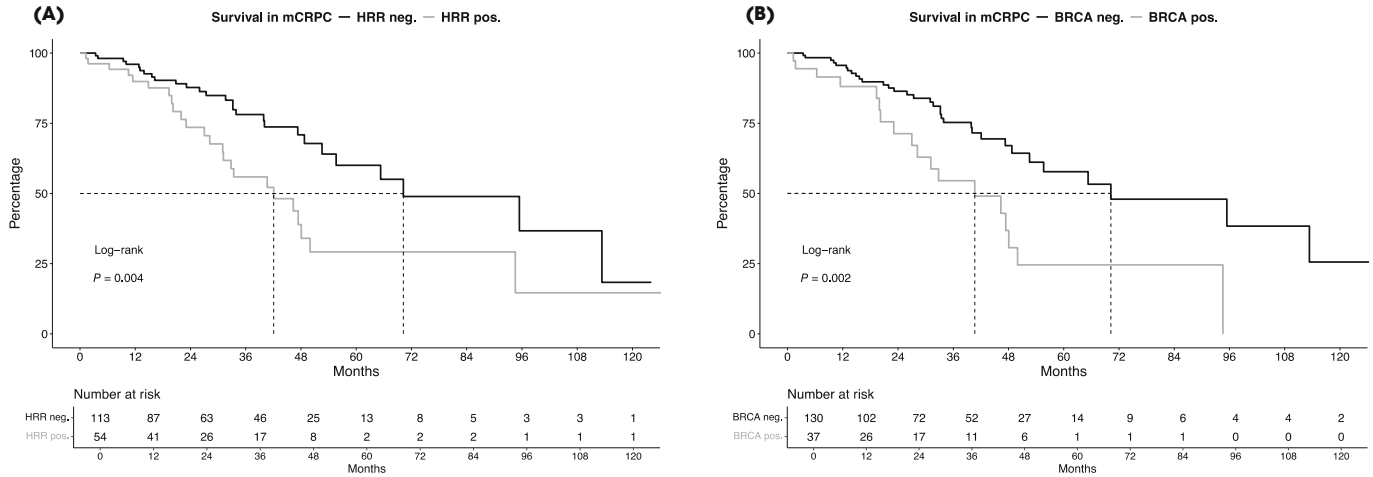


Fig. 2 The OS in patients with mCRPC comparing (**A**) HRR-positive (pos.) vs -negative (neg.) and (**B**) *BRCA*1/2-pos. vs -neg. patients.



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HR of 2.48 ($P = 0.001$). After controlling for patient and tumour characteristics in multivariable Cox regression models, *BRCA* also independently predicted worse OS in mCRPC (HR 2.16, $P = 0.02$).

The PARPi Treatment Effect

Exploring the effect of PARPi treatment in mCRPC (Fig. 3), patients with *BRCA* alterations and no PARPi treatment harboured worse median OS (33 months) vs *BRCA*-positive patients with mCRPC treated with PARPi (48 months) vs *BRCA*-negative patients (70 months, $P < 0.01$). No differences were seen in OS comparisons between tissue vs liquid biopsy tested HRR- or *BRCA*-positive patients.

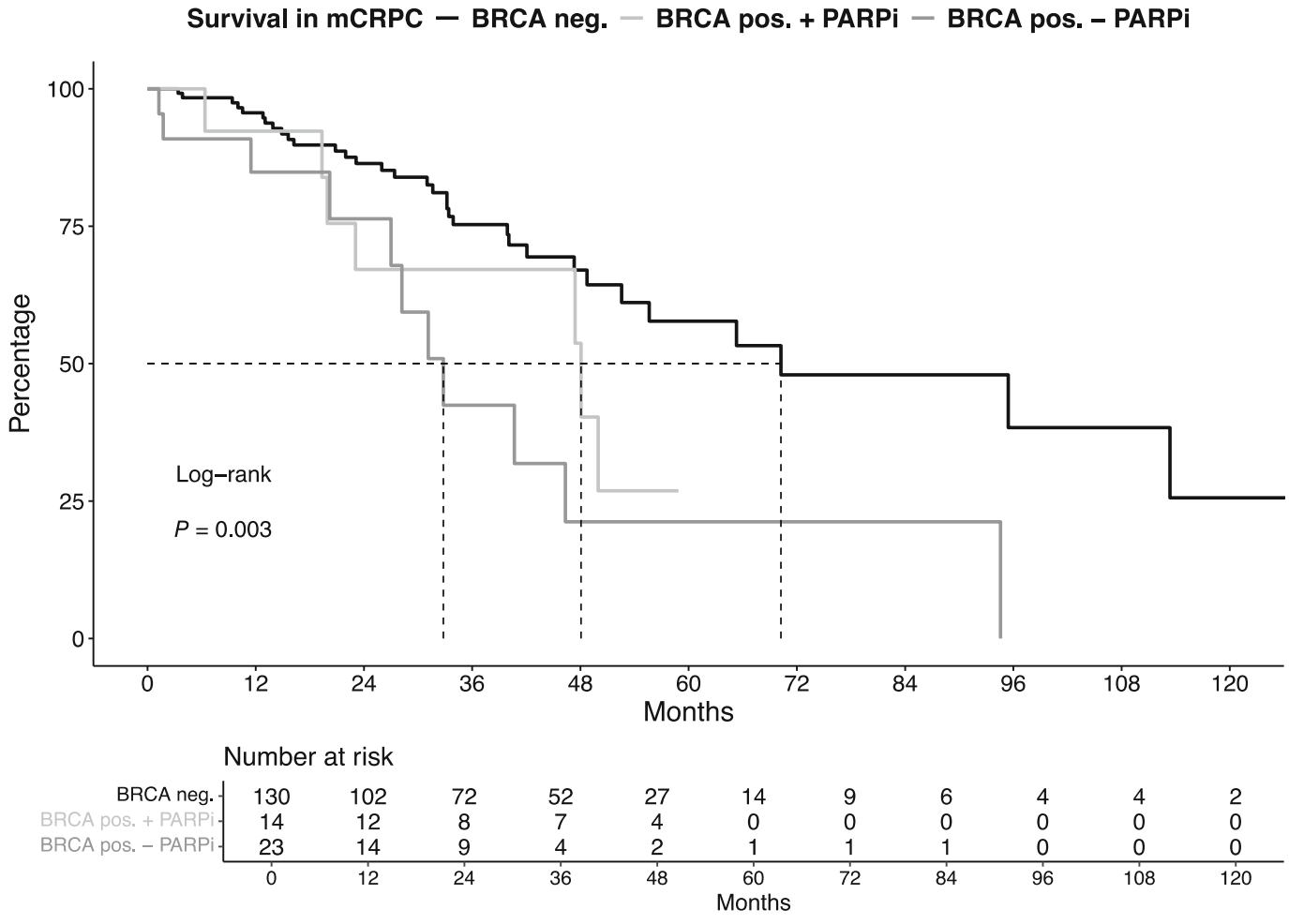
In uni- and multivariable Cox regression models, patients with mCRPC with *BRCA* alterations and no PARPi treatment harboured significantly worse OS (univariable HR 3.05, $P = 0.001$; multivariable HR 2.77, $P < 0.01$), while patients with mCRPC with *BRCA* alterations and PARPi treatment did not show OS differences, compared to *BRCA*-negative patients in uni- and multivariable Cox regression models (both $P \geq 0.12$).

Discussion

We hypothesised that patient and tumour characteristics, as well as OS differs significantly between HRR-positive and *BRCA*-positive patients with metastatic prostate cancer, relative to those who test negative. Moreover, we also hypothesised that PARPi treatment may have a positive impact on OS in a real-world setting. We addressed these questions relying on our institutional metastatic prostate cancer database and made several important observations.

First, we observed that of all screened patients with metastatic prostate cancer, 31% harboured a HRR alteration. Moreover, we found that the most common HRR alterations were *BRCA*1/2 (66%), followed by *ATM* (10%) and *CHEK2* (8.2%). These observations are in agreement with previous

Fig. 3 The OS of patients with mCRPC comparing *BRCA*1/2-positive (pos.) patients treated with a PARPi vs *BRCA*1/2-pos. patients without PARPi vs *BRCA*1/2-negative (neg.) patients.



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publications. For example, a recently published real-world multicentre study of 38 centres in Spain and Italy also found a HRR prevalence of 30.6% in patients with mCRPC, of which 43% were related to *BRCA* alterations [14]. Similarly, *ATM* alteration was the second most common HRR alteration at 8.4%. Moreover, in another recently published study by Uemura et al. [15], enrolling data from 143 patients with mCRPC of 24 Japanese institutions, also a HRR prevalence of 35.7% was reported. However, the most common HRR alteration was *CDK12* (13.3%), followed by *BRCA 2* (12.6%), *ATM* (5.6%) and *CHEK2* (2.1%). These observations may indicate that HRR alterations are frequently observed in patients with metastatic prostate cancer in real-world settings and are comparable to previous phase III trial published data (e.g., TALAPRO-2 study: 30.1% HRR germline alterations [7]). However, the proportions of different HRR alterations may differ according to geographical region and type of sampling. However, in the present cohort 36% of all eligible patients had blood-based and tumour tissue-based tests and some of the tissue tests were only testing for *BRCA* alterations, which may have altered the rate of HRR and especially *BRCA*-positive patients. Nevertheless, the present data show some evidence, that combining liquid biopsy and tissue-based testing might be the best approach for identifying most of the suitable patients for PARPi therapies [16,17].

Second, we observed no differences in time to mCRPC of patients with mHSPC, when HRR-positive vs -negative, as well as *BRCA*-positive vs -negative patients were compared. In these compared cohorts, time to CRPC was relatively short (16.8–17.0 months), compared to previous published reports on time to castration resistance in real-world settings or clinical trials [18–21]. However, exploring patient characteristics of our HRR-tested cohort to other HRR-reporting real-world data such as the one from Olmos et al. [14], our included patients harboured higher rates of unfavourable Gleason score 8–10 (80% vs 63%) and primary metastatic prostate cancer (79% vs 47%), which may translate into shorter time to castration resistance. Previous studies have also shown that in general patients with prostate cancer with *BRCA* alterations harbour more aggressive phenotypes, such as higher proportions of Gleason Score 8–10, which was also observed in the present study [22].

Third, when OS was compared, we found significant worse OS for HRR- and *BRCA*-positive patients in the setting of mHSPC, as well as for mCRPC. Specifically, patients without HRR and *BRCA* alterations extensively exceeded the median OS of patients with HRR alteration. However, only in patients with mCRPC did HRR and *BRCA* alterations influence OS in additional multivariable Cox regression models. These observations may indicate that the effect of HRR alterations is more pronounced, when disease has progressed to mCRPC and the effect of the primary treatment for mHSPC, which gains in general the longest absolute OS benefit [23,24], has lost its cancer-control effect. This hypothesis may be supported by the theory of 'BRCAness' induction by ARSI pretreated patients with mCRPC, as primary treatment may affect the response to secondary mCRPC outcomes [25-28]. However, the role of HRR/*BRCA* alterations in mHSPC still need to be determined by ongoing phase III trials [7,27]. Our findings may be of clinical importance as they support the drive and need for HRR alteration testing in early disease stages of advanced prostate cancer. However, the rate of HRR testing in the real-world clinical scenario still remains only at ~50% [29]. Nonetheless, due to its prognostic value and approximation of treatment responses, we believe that HRR/*BRCA* testing is crucial in these patients.

Finally, we found that only 30.0% and 34% of HRR- and *BRCA*-positive patients, respectively, were treated with PARPi and only 4.4% of HRR-negative patients. Conversely, we observed that the treatment with a PARPi in *BRCA*-positive patients extended the median OS compared to BRCA-positive patients without PARPi treatment. The low rate of PARPi administration may be explained by the fact that the first European Medicines Agency (EMA) approval for olaparib monotherapy was only allowed for *BRCA*1/2-positive tested patients with mCRPC after ARSI, while now the combination of olaparib plus abiraterone, as well as talazoparib plus enzalutamide is approved irrespectively of HRR status [7–9]. Nonetheless, our findings indicate that the administration of PARPi may almost equalise the OS disadvantage in *BRCA*-positive patients towards the OS of *BRCA*-negative patients with mCRPC in a real-world setting. Hence, greater emphasis should be placed on prompt testing and initiation of PARPi therapy in real-world clinical settings for patients positive for HRR/*BRCA* alterations, where—according to our data—it does not make any difference if HRR/*BRCA* alterations are found by liquid biopsy or tissue testing.

Our study has limitations and needs to be considered in the light of its single-centre and retrospective design. Moreover, there is currently no consensus on HRR testing regarding its time point, kind of test (tumour tissue vs liquid biopsy) or germline vs somatic testing. Due to the real-world cohort analysed within the present study, unfortunately no further distinction regarding these subgroups could be made. Therefore, the present data of HRR alterations may be affected by a heterogeneity of sampling and quality in addition to the heterogeneity of the tests used and their included HRR genes, coverage of target gene regions, and databases used for pathological test interpretation. However, the study aimed to provide and reflect clinicians in a real-world setting. Our incidence of positive- or negative-HRR/*BRCA* tested patients may be influenced by patients receiving more than one testing or tissue and liquid biopsy HRR testing, which may not reflect all real-world scenarios in urological centres. However, the aim of the study was to

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explore real-world outcomes of patients with HRR alterations, with currently available pathological data reports. Furthermore, only a limited follow-up was available for some patients, which might have influenced some of the results. Finally, some of the analysed subgroups may be restricted for further sensitivity analyses due to limited sample size.

Taken together, the incidence of HRR alterations in a real-world setting in Germany is high and comparable to other countries. However, patients with HRR and *BRCA* alterations in particular harbour worse OS when mCRPC status is reached. The administration of PARPi prolongs OS in *BRCA*-positive patients with mCRPC.

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Disclosure of Interests

The authors declare no competing interests.

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None.

Data Availability Statement

Data are available for bona fide researchers who request it from the authors.

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Abbreviations: ARSI, androgen receptor signalling inhibitor; *ATM*, Ataxia-telangiectasia mutated kinase; *BRCA*, BReast CAncer gene; *CDK12*, cyclin-dependent kinase 12; *CHEK2*, checkpoint kinase 2; *FANCA*, Fanconi anaemia complementation Group A; HR, hazard ratio; HRR, homologous recombination repair; ID, identifier; IQR, interquartile range; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; OS, overall survival; PARPi, inhibitor of poly (ADP-ribose)-polymerase.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Time to CRPC in (A) HRR-positive vs -negative patients with mHSPC and (B) *BRCA*1/2-positive vs -negative mHSPC.

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