Olaparib for Chinese Metastatic Castration-resistant Prostate Cancer: A Real-World Study of Efficacy and Gene Predictive Analysis

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Research Article

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Abstract

Objective: To evaluate the real-world effectiveness and gene predictive analysis of olaparib in Chinese patients with metastatic castration-resistant prostate cancer (mCRPC) .

Methods: A multicenter, retrospective, real-world study was conducted by involving Chinese patients with mCRPC from December 2017 to June 2021. Homologous Recombination repair (HRR)gene mutation (HRRm) status was identified using targeted next-generation sequencing (NGS). The primary endpoint includes prostate-specific antigen (PSA) response rate (PSA_{50}). Secondary end points include PSA progression-free survival (PSA-PFS), exploratory endpoints include PSA_{50}, and PSA-PFS in HRRm-negative patients with variants of unknown significance (VUS). Survival rates were analyzed using Kaplan–Meier (KM) plot.

Results: A total of 39 eligible patients with a median age of 65 (interquartile range [IQR]: 59.5-69.5) years were included in the study. Overall, 40% (12/30) of the patients with mCRPC achieved PSA_{50} and the median PSA-PFS was 3.1 months (95% Confidence interval [CI]: 2.4-7). Furthermore, higher PSA_{50} rate and longer PSA-PFS were observed in HRRm-positive patients (PSA_{50}: 50% [7/14]; median PSA-PFS: 5.3 months, 95% CI: 3.73–10). Among the HRRm-positive patients, those harboring the BRCA2 aberrations experienced best clinical efficacy (PSA_{50}: 55.5% [5/9] and median PSA-PFS [95% CI]: 9.5 months [4.3, NA]). Clinical benefit was also observed in HRRm-negative patients (PSA50: 31.3% [5/16]; median PSA-PFS [95% CI]:2.05 months [1.5,8]), wherein most patients with a PSA_{50} response were carrying VUS mutations (PSA_{50}: 50% [4/8]; median PSA-PFS [95% CI]: 2.75 months [1.27, NA]). In one patients with mutation in the ATR gene, the PSA level decreased by 62%.

Conclusion: Olaparib improved PSA response and prolonged PSA-PFS in Chinese mCRPC patients especially in those carrying HRR mutation. Among the HRR genes, patients with *BRCA2* mutation showed the best clinical benefit. Besides, some patients carrying HRR VUS alternations and other DNA damage response (DDR) gene mutations also showed response to olaparib treatment, indicating that the clinical benefits observed in HRR negative group were driven by VUS and other DDR gene mutation. However, this should be further explored in the future, and more molecular functional studies are needed to reclassify VUS mutations for better clinical treatment decision-making and management of mCRPC.

Introduction

Metastatic castration-resistant prostate cancer (mCRPC) is a heterogeneous disease generally associated with aberrations in the DNA damage response (DDR) genes leading to poor clinical outcomes.[1] However, the therapeutic landscape of mCRPC has rapidly evolved with the advancement in sequencing techniques such as targeted next-generation sequencing (NGS) for the identification of mutations that could guide the application of targeted therapy. NGS also revealed that mCRPC tumors has a complex genomic landscape wherein genomic alterations were observed in pathways that are not related to androgen receptors and which could be targeted for therapy.[2,3] Meanwhile, several studies from China demonstrated that there are a large number of patients with prostate cancer carrying mutations in homologous recombination repair (HRR) genes.[4,5] In addition, 15% to 30% of cases were found with germline or somatic mutations in HRR genes (including *BRCA1/2, ATM* and *CHEK2*) and have more aggressive disease and higher mortality than those with proficient HRR functionality.[6–9] Therefore, the high prevalence of these mutations has led to the National Comprehensive Cancer Network (NCCN) recommending germline/somatic testing of HRR gene alterations in all patients with metastatic prostate cancer.[10]

Recently, studies have demonstrated that the presence of such genetic aberrations may enhance the sensitivity of prostate cancer to poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors .[11] The PROfound trial which evaluated the efficacy of olaparib in prostate cancer patients with HRR gene aberrations demonstrated significant increase in progression free survival in olaparib treated patients in comparison to standard of care. [1] Based on the results of the PROfound trial, the NCCN guideline recommended treatment with olaparib for patients with HRR-mutated mCRPC.[10] Subsequently, in May 2020, the Food and Drug Administration approved olaparib in adult patients with mCRPC with germline/somatic HRR gene alterations.[12] Furthermore, the National Medical Products Administration (NMPA) approved olaparib in mCRPC patients carrying germline and/or somatic BRCA1/2 mutations who have progressed after prior treatment with enzalutamide or abiraterone in June 2021. Likewise, several studies demonstrated the differential clinical outcomes with olaparib in patients with HRR gene mutated mCRPC such as *BRCA1/2 orATM*.[13,14] Despite these remarkable observations, the current clinical decisions are guided mainly by evidence from western populations. Besides, genomic study in Chinese patients with metastatic prostate cancers suggests that germline mutation spectrum of HRR genes is similar among Chinese and Western population.[4] However, there are some differences in the somatic mutation spectrums where the prevalence of BRCA2 (13%) and CDK12 (15.4%) mutations in

tumor tissue is higher in Chinese mCRPC population, and patients with CDK12 defects showed rapid disease progression after abiraterone treatment while patients with BRCA2 defects showed marked response to PARP inhibitors and platinum based chemotherapy.[15,16] Furthermore, there still lack of real-world evidence from China evaluating the effectiveness of olaparib in patients with mCRPC. Therefore, this real-world study was undertaken to evaluate the effectiveness of spontaneous use of olaparib in Chinese patients with mCRPC.

In addition, there are no hotspot mutations in HRR genes and the classification of the pathogenicity of HRR mutations are based on the statistics in research reports and the degree to which the genetic change is predicted to alter the structure and function of the encoded protein, and classified as pathogenic, likely pathogenic, variants of uncertain significance(VUS), likely benign and benign.[17] HRR mutations which have not been reported previously or conflict evidence existed on the functionality effect of encoded protein are classified as VUS, and clinical decision cannot be made if patients carrying VUS mutation. However, the proportion of the VUS in HRR genes is high due to the lack of evidence, where 30% of genetic tests reported VUS alterations,[18] which leads to confusion in clinical practice, and needs to be further explored desperately.

Methods

Study Design and Data Collection

A multicenter, retrospective, real-world study was conducted by including Chinese patients with mCRPC. Patients' demographic and clinical data were obtained from Renji Hospital affiliated to Shanghai Jiaotong University School of Medicine, the Tenth People's Hospital affiliated to Shanghai Tongji University, and the First affiliated hospital of Wenzhou Medical University, China, from December 2017 to June 2021. The HRR gene mutation status (*BRCA1/2*, *ATM, PALB2, CDK12, RAD54L, RAD51B,,RAD51C,RAD51D, FANCL, CHEK1/2, BRIP1,* and *BARD1*) of patients with mCRPC were confirmed by targeted NGS using deep targeted sequencing of plasma circulating tumor DNA (ctDNA) or tumor tissue. Furthermore, patients who received previous olaparib (at least 1 month) mono or combo therapy spontaneously and no prior treatment with other PARP inhibitors were included in the study. In addition, data for systemic therapy initiated after the onset of mCRPC were obtained. For each systemic therapy, the data on treatment line and the decline in PSA ≥50% from baseline (PSA_{50}) were obtained. All centers participating in the study obtained approval from the local institutional review board before data abstraction.

Next-Generation Sequencing and Bioinformatic Analysis

The targeted NGS test of all tissue/blood samples collected from each individual patient was performed at Glorious Med Clinical Laboratory (Shanghai) Co, Ltd. Targeted sequencing and bioinformatic analysis, including the identification of germline and somatic mutation and copy number alteration, were conducted as described previously by Dong et al.[15] The pathogenicity of identified gene variants was interpreted by following the general guideline of germline mutation and somatic mutation classification.[19,20] All loss-of-function alterations of HRR genes were coded as deleterious or suspected deleterious, including deletion, nonsense mutations, frameshift, and splice site alterations. Otherwise, unless specifically designated as deleterious in the ClinVar database, missense mutations were considered as VUS. Patients carrying deleterious/suspected deleterious mutation on HRR gene (*BRCA1/2, ATM, PALB2, CDK12, RAD54L, RAD51B/C/D, FANCL, CHEK1/2, BRIP1,* and *BARD1)* were considered as the HRRm-positive group and others were considered as the HRRm-negative group, which includes patients carrying VUS on HRR gene (HRRm-negative VUS) or those carrying other DDR defects or no deleterious mutations identified (HRR-negative other).

Treatment and Outcomes

Patients who received systemic therapy with olaparib either as monotherapy or in combination with abiraterone spontaneously were considered and analyzed individually. The primary end point includes PSA response rate (defined as post-medicine PSA decline >50% from baseline at 12 weeks). The secondary end points include PSA progression-free survival (PSA-PFS), the exploratory endpoints included PSA response rate, and PSA-PFS in HRR-negative VUS patients. PSA-PFS was defined as the time from the beginning of treatment with olaparib to the first confirmation of PSA progression (defined as testosterone meets the castration level [<50 ng/dL h or <1.7 nmol/L] and blood PSA rises) or death (any cause), whichever occurs first.

Statistical Analysis

Continuous variables were represented using values of interquartile range (IQR). Categorical variables were represented in percentages. The reduction in PSA levels >50% from the baseline at 12 weeks was considered for PSA remission and 95% confidence interval (CI) was calculated using Binomial “exact” calculation. Survival rates were calculated using the Kaplan–Meier (KM) plots. The difference in hazards function was analyzed using the Cox proportional hazard regression analysis, and the results were expressed as hazard ratio (HR) and 95% CI. All the analyses were performed with R software, version 3.5. The sorting intolerant from tolerant (SIFT) algorithm was used for predicting the deleterious effect of coding variants on protein function.

Results

Patient Characteristics and Genomic Landscape

A total of 39 eligible patients aged 65 (IQR: 59.5–69.5) years with were included in the study. Their data on demographics, clinicopathological characteristics, and prior treatments were presented in Table 1. At the time of diagnosis, the PSA level (IQR) was 110 (51.5–110) ng/mL, and 81.8% patients were primarily diagnosed with bone metastasis. Furthermore, 87.2% (n = 34) of the patients have received prior new hormonal agent therapy and 61.5% (n = 24) of the patients have received docetaxel treatment. Besides, olaparib was mainly used in the second line and later phases of treatment predominantly as monotherapy. Moreover, gene test by NGS revealed HRRm-positive results in 18 patients, and the most commonly detected HRR aberrations were in *BRCA2* (n = 10), *ATM* (n = 3), and *CDK12* (n = 2). In addition, HRRm-negative VUS alterations were detected in 8 patients, and the most common VUS mutations detected were in *BRCA2* (n = 3) and *ATM* (n = 3).

Table 1

Clinicopathological Characteristics

	Overall	HRR Positive	HRR Negative	
			HRR-Negative VUS	HRR-Negative Other
Sample size (n)	39	18	8	13
Age (IQR), years	65 (59.5–69.5)	64 (59.5–66)	66 (59–69.75)	66 (59.25–71.5)
≥65 years, n (%)	19 (51.4%)	7 (18.9%)	4 (50%)	8 (61.5%)
PSA (IQR), ng/mL	110 (51.5–110)	105 (52.8–110)	79 (34.5–852.5)	110 (78.05–257.15)
Gleason score				
<8	6 (16.2%)	2 (11.8%)	1 (14.3%)	3 (23.1%)
≥8	31 (83.8%)	15 (88.2%)	6 (85.7%)	10 (76.9%)
Metastasis at primary diagnosis, n (%)	29 (87.9%)	16 (94.1%)	4 (80%)	9 (81.8%)
Bone metastasis, n (%)	27 (81.8%)	14 (82.4%)	4 (80%)	9 (81.8%)
Previous treatment before Olaparib				
Second-generation androgen receptor inhibitors, n (%)	34 (87.2%)	15 (83.3%)	6 (75%)	13 (100%)
Docetaxel, n (%)	24 (61.5%)	12 (66.7%)	5 (62.5%)	7 (53.8%)
Platinum-based chemotherapy, n (%)	4 (10.3%)	1 (5.6%)	1 (12.5%)	2 (15.4%)
Olaparib treatment				
Olaparib monotherapy	33 (84.6%)	15 (83.3%)	6 (85.7%)	12 (85.7%)
Olaparib + abiraterone	6 (15.4%)	3 (16.7%)	1 (12.5%)	2 (15.4%)

HRR, homologous recombination repair; IQR, interquartile range; PSA, prostate-specific antigen; VUS, variants of uncertain significance.

Olaparib Showed Remarkable Clinical Outcomes in Chinese Patients With mCRPC

PSA_{50} response and PSA-PFS to olaparib-based treatment were evaluated in all patients. In total, 40% (12/30) of the patients with available data achieved a PSA_{50} response, and the response rate is higher in HRRm-positive patients (50% [7/14]) than in HRRm-negative patients (31.3% [5/16]; Fig. 1A and B). Meanwhile, PSA_{50} responders with HRRm-positive alterations majorly harbor *BRCA2* mutations (n = 5) followed by *CDK12* mutation (n = 1) and *RAD51C* mutation (n = 1), whereas PSA_{50} responders in the HRRm-negative group were mainly carrying HRR VUS mutations in BRCA2 and ATM genes. Overall, the median PSA-PFS in 34 patients with available data was 3.1 months (95% CI: 2.4,7). The median PSA-PFS was higher in the HRRm-positive group (5.3 months [95% CI: 3.73,10]) compared with the HRRm-negative group (2.05 months [95% CI: 1.5–8]; [HR: 0.523; 95% CI: 0.265,1.03]; Fig. 2A). Notably, a remarkable clinical benefit was observed in patients with *BRCA2* mutation (median PSA-PFS: 9.5 months [95% CI: 4.3, NA]; Fig. 2B). The clinical benefits in HRR negative group were mainly observed in patients with HRR VUS mutations and other DDR mutations which elucidated in the following data.

Clinical Benefits of Olaprib Observed in part of Patients With HRR VUS Mutations

In the present study, there are 8 patients with HRRm-negative VUS mutations and 2 patients with other DDR gene mutations. The mutation sites and effectiveness data of patients with HRR VUS mutations were presented in Table 2. A median PSA-PFS (95% CI) of

2.75 months (1.27, NA) and a PSA_{50} response rate of 50% (4/8) were observed in these patients (Fig. 1C). Particularly, 4 patients with *BRCA2* p.L3125P, *BRCA2* p.Q1551K, g*ATM* p.Y171C and gATM p.F1036L exhibited longer PSA-PFS (Table 2). Mutation plots showing the placement of the mutation on *BRCA2* and *ATM* are depicted in Figure 3. The mutation on *BRCA2* gene was located at the oligonucleotide/oligosaccharide-binding domain 3 and repeat domain (Fig. 3A and B), whereas, the mutation on *ATM* was located at the telomere length maintenance-DNA damage repair domain (Fig. 3C). Additionally, bioinformatics prediction algorithm 'sorting intolerant from tolerant' (SIFT) revealed all 3 VUS mutations have damaging impact on the protein structure, indicating its most likely pathogenic nature and clinical relevance, consistent with their better sensitivity to olaparib. In one patient carrying deleterious gene aberration in ATR p.K2106fs, a PSA remission of 62% was observed.

Table 2

HRR-Negative VUS Mutation Sites and Their Effectiveness Data

Mutation	PSA-PFS (months)	PSA Response Rate (%)	SIFT Prediction of Protein Function
gBRCA2 p.L3125P	8	−83.5	Damage
BRCA2 p.Q1551K	21.4	NA	Damage
gATM p.Y171C	3.6	−70.6	Damage
gPALB2 p.P405A	1.5	100	Tolerated
gATM p.Q2802R	0.5	228.6	Tolerated
gCDK12 p.R663C	1.27	−61.2	Not score
gBRCA2 p.H2090R	1.2	135	Tolerated
gATM p.F1036L	4	−91	Tolerated

HRR, homologous recombination repair; PSA, prostate-specific antigen; PSA-PFS, prostate-specific antigen progression-free survival; SIFT, sorting intolerant from tolerant; VUS, variants of uncertain significance.

Discussion

Genomic profiling is increasingly used for routine clinical management of prostate cancer. Genomic profiling with NGS has revealed mCRPC to be heterogenous and has also made it feasible for personalized targeted therapy for specific biomarkers.[7] In the current real-world study, olaparib showed remarkable clinical outcomes in Chinese patients with mCRPC, especially in patients harboring HRR gene aberrations. The results from the current study are in line with the earlier reports from larger prospective trials including the TOPARP-A, TOPARP-B and PROfound trial in which olaparib demonstrated prolonged radiologic progression-free survival (rPFS) in mCRPC patients with HRR mutations.[11, 21] In the PROfound trial, the median rPFS was significantly longer in the patients with at least 1 aberration in HRR genes than in the control group (enzalutamide or abiraterone; rPFS: 5.8 months vs 3.5 months; HR: 0.49; 95% CI: 0.38–0.63; P<0.001). Further 43% (66/153) of patients carrying at least 1 aberration in the BRCA1/2 or ATM gene treated with olaparib had a PSA_{50} response while only 8% of patients in the control group had a PSA_{50} response.[1]

Several prospective genomic studies demonstrated that men with BRCA1/2 mutations have increased risk of early-onset and clinically significant prostate cancer.[22–24] Furthermore, germline BRCA1/2 status is an independent prognostic factor for prostate cancer outcome, where patients carrying BRCA1/2 mutation are associated with high Gleason score, late TNM stage at diagnosis, early distant metastasis, and low 5-year survival.[25] In a prospective cohort study (PROREPAIR-B), cause specific survival of mCRPC patients with BRCA1/2 mutation was significantly less (17.4m vs 33.2m, p=0.027) in comparison to patients with wild type after receiving standard therapy (abiraterone or doxetaxel).[26] However, in the current study, mCRPC patients harboring *BRCA2* mutations experienced superior clinical outcomes with olaparib monotherapy (PSA-PFS: 9.5 months, 95% CI: 4.3, NA) which was in accordance to another real-world study wherein patients harboring BRCA 1/2 gene variants had a significantly higher rate of PSA remission and longer PFS than those with variants in other HRR genes.[27]

Several studies substantiated that *BRCA1/2* aberrations are a strong predictor of a favorable response to PARP inhibitors. But in case of prostate cancer, an increase in the frequency of the incidence of VUS in *BRCA1/2* gene was reported.[28] Since the effects of the VUS on the function of the encoded protein or disease risk is unknown, this poses a major challenge for genetic counseling and clinical management, which may require dynamic changes in the reporting of results for clinical decision making ("upgraded" to pathogenic or "downgraded" to benign).[29–31] However, the findings from the current study demonstrated that patients harboring HRR VUS mutations exhibited a high PSA response rate and prolonged PSA-PFS after olaparib treatment, indicating that patients harboring HRR VUS mutations may benefit from olaparib treatment, which need further confirmation. There are several molecular- or cellular-level functional assays (such as cellular survival and viability assay, DNA recombination repair assay, genomic instability assay, and drug sensitivity assay) with high sensitivity and specificity that allow accurate assessment of the effects of VUS mutations on the encoded protein function.[29,30,32] Despite considerable efforts to determine the pathogenicity of VUS mutations using multiple functional assays, for most VUS, this is not successful because of the lack of general consensus in clinical practice and evidence on the clinical efficacy of these mutations.[31,33] To the best of our knowledge, this was the first study to emphasize on the clinical relevance of HRR VUS alterations in Chinese patients with mCRPC,; the findings from the current study may bring new evidence to the reclassification of VUS mutations in clinical practice and olaparib maybe considered for mCRPC patients carrying VUS alterations and without effective therapy regimen available.

Another interesting observation in the study is some patients exhibited prolonged survival benefits defined as PFS >1 year; the characteristic of these patients is listed in Table 3. Several common points are identified. Four patients carrying *BRCA2* mutations (3 patients in the HRRm-positive group and 1 patient with HRR VUS defect) received olaparib and abiraterone combination therapy either as 2L or 3L therapy. In addition, in 1 patient (patient ID: WY) with HRR VUS alteration g*ATM* p.Y171C, PSA level raised after 4 months of treatment and declined after 9 months and demonstrated lower PSA-PFS (4 months). However, the patient exhibited prolonged survival with olaparib treatment (overall survival: 38 months; Table 3). Although PARP inhibitors have demonstrated the clinical effectiveness in several kinds of tumors with underlying HRR deficiencies, there is now biologic and early clinical evidence to support their use in other molecular subsets of cancer, including DDR defects.[34,35] At this juncture, another noteworthy finding was observed in our study: prolonged PSA-PFS (13 months) and PSA response were observed in a patient harboring DDR defect in the ATR loci (*ATR* p.K2106fs; Table 3), suggesting that other DDR gene aberrations may also confer sensitivity to olaparib treatment. The role of ATR in DNA repair pathway pertains to both single and double strand break repair.[36] Mutations in ATR loci is rarely reported in clinical studies and a previous meta-analysis evaluating the role of DDR mutations in 77 genes reported a high number of studies with unknown ATR gene status.[37,38] Recently, a mounting body of evidence from in vitro and in vivo studies indicates that PARP inhibitors in combination ATR inhibitors can be used across a wide spectrum of cancers, and these findings lead to early-phase clinical trials combining *ATR* and PARP inhibitors (NCT02576444, NCT02723864, NCT03787680 [TRAP-trial], and NCT03682289).[39] However, larger prospective trials are required to substantiate the effectiveness of PARP inhibitors in subset of patients with other DDR defects.

Table 3

Patient Characteristics and Clinical Outcomes of Patient Exhibiting Prolonged Survival Benefits

Patient ID	RJ119	SY4	SY5	RJ62	WY	RJ103
Age (years)	42	59	70	61	69	70
PSA at diagnosis	>100	11.92	30	55	unknown	>100
Gleason score	9	10	9	8	9	8
Distant metastasis at first diagnosis	Multiple bone metastases	Multiple lymph nodes metastases	Multiple bone metastases	Multiple bone metastases	Multiple bone metastases	Multiple bone metastases
ADT treatment duration (months)	12	1	7	60	9	48
mCRPC 1L	Abiraterone	Docetaxel	Abiraterone	Abiraterone	Enzalutamide	Abiraterone
1L PSA-PFS	unknown	Primary resistant	5.7	10	NO effect	12
mCRPC 2L	Abiraterone + olaparib	Radiotherapy + abiraterone	Docetaxel	Docetaxel	Docetaxel	Olaparib
2L PSA-PFS	**16**	Unknown	4	2	Unknown	13
mCRPC 3L	NA	Abiraterone + olaparib	Abiraterone + olaparib	Olaparib	Olaparib	
PSA-PFS (m)	**16***	**30***	**21.4**	**16**	**4**	**13**
PSA response rate	**−89.5%**	Unknown	Unknown	−32%	−**70.6%**	−**62.2%**
Overall survival (m)	16*	30*	**27.4**	**39.5**	**38**	Unknown
Mutation sites	gBRCA2 splicing	BRCA2:p.K2849fs	BRCA2p.Q1551K (0.5%)	BRCA2:p.N1784fs	gATM p.Y171C	ATR p.K2106fs (0.72%)
Biomarker status	HRRm positive	HRRm positive	HRR VUS	HRRm positive	HRR VUS	DDR defect

ADT, androgen deprivation therapy; DDR, DNA damage repair; HRR, homologous recombination repair; mCRPC: metastatic castration-resistant prostate cancer; NA, not available; PSA-PFS, prostate-specific antigen progression-free survival; VUS, variants of uncertain significance.

PSA-PFS and overall survival were calculated from the starting of olaparib treatment to the end of follow-up, * indicated that patients were in progress-free status or alive until the end of follow-up.

Despite these interesting findings, our study has certain limitations. First, the retrospective nature as well as relatively small sample size limit the interpretation of the negative results. Second, lack of overall survival and safety data that indicate that systemic and intense follow-up system need to be established in the future.

Conclusions

In conclusion, based on the PSA remission rate and PSA-PFS, it is evident that clinical benefits of olaparib was notable in mCPRC patients, where a remarkable clinical outcome was observed in patients harboring HRR mutations, especially *BRCA2* mutation. In addition, PSA response and prolonged PSA-PFS were observed in some patients carrying HRR VUS mutations or alterations in other DDR genes, olaparib maybe considered for these patients without effective therapy regimens available. Though this study substantiates the

clinical evidence for the reclassification of these VUS sites, further functional studies and larger prospective trials are needed in this direction to confirm the findings.

Abbreviations

mCRPC: Metastatic castration-resistant prostate cancer

HRR: Homologous recombination repair

VUS: Variants of uncertain significance

PSA: Prostate-specific antigen

PSA-PFS: Prostate-specific antigen progression-free survival

NGS: Next-generation sequencing

Declarations

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Conflict of Interest

No conflict of interest claimed.

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Figures

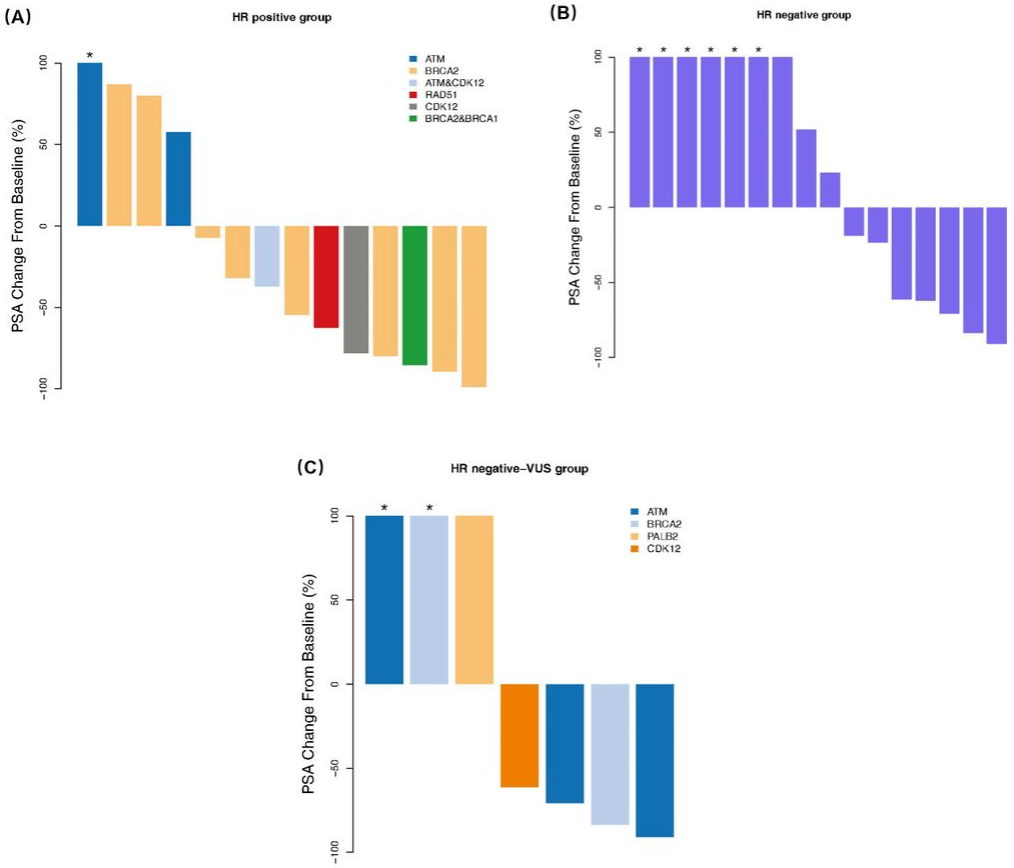

Figure 1. PSA remission rate: (A) HRRm-positive group, (B) HRRm-negative group, and (C) HRRm-negative VUS group. HRR, homologous recombination repair; PSA, prostate-specific antigen ; VUS, variants of uncertain significance; * indicates PSA change>100%.

Figure 1

Please See image above for figure legend.

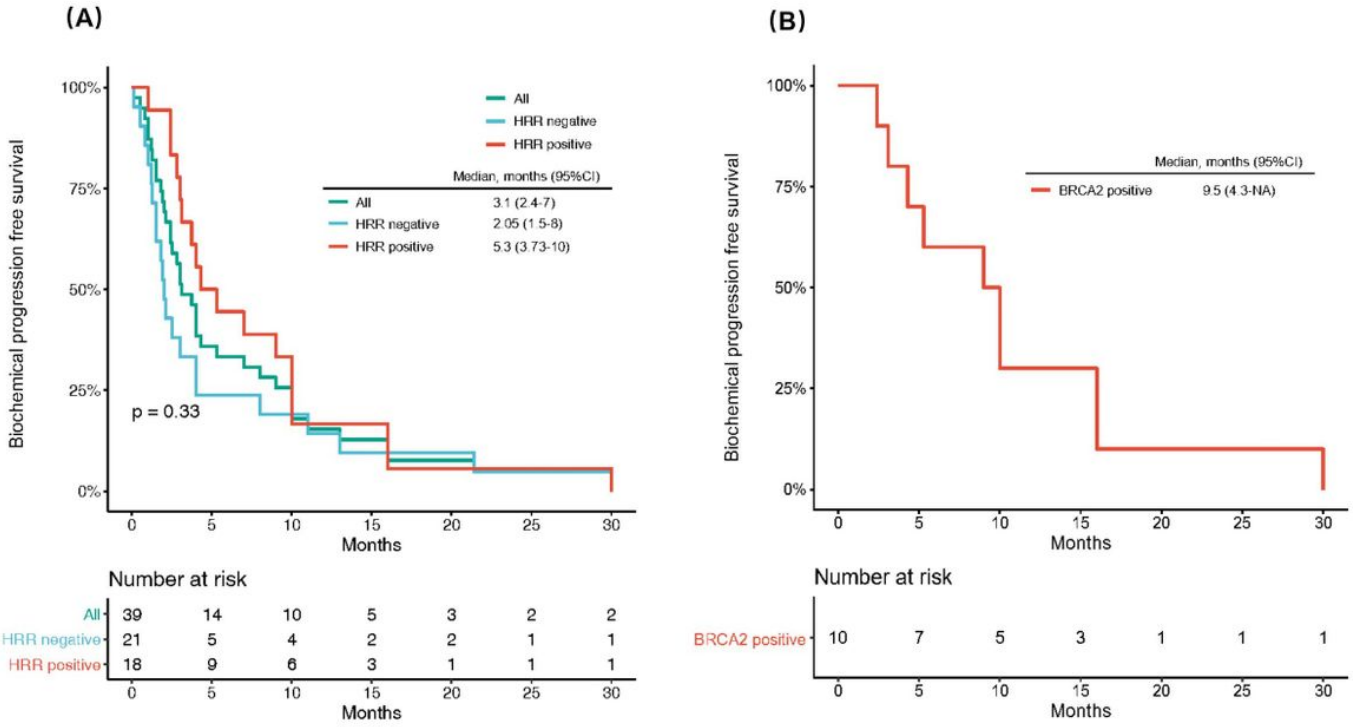

Figure 2. Kaplan–Meier curves for PSA-PFS: (A) overall group, HRRm-positive subgroup, and HRR-negative subgroup and (B) HRRm-positive patients with BRCA2 mutations.

HRR, homologous recombination repair; PSA-PFS, prostate-specific antigen progression free survival

Figure 2

Please See image above for figure legend.

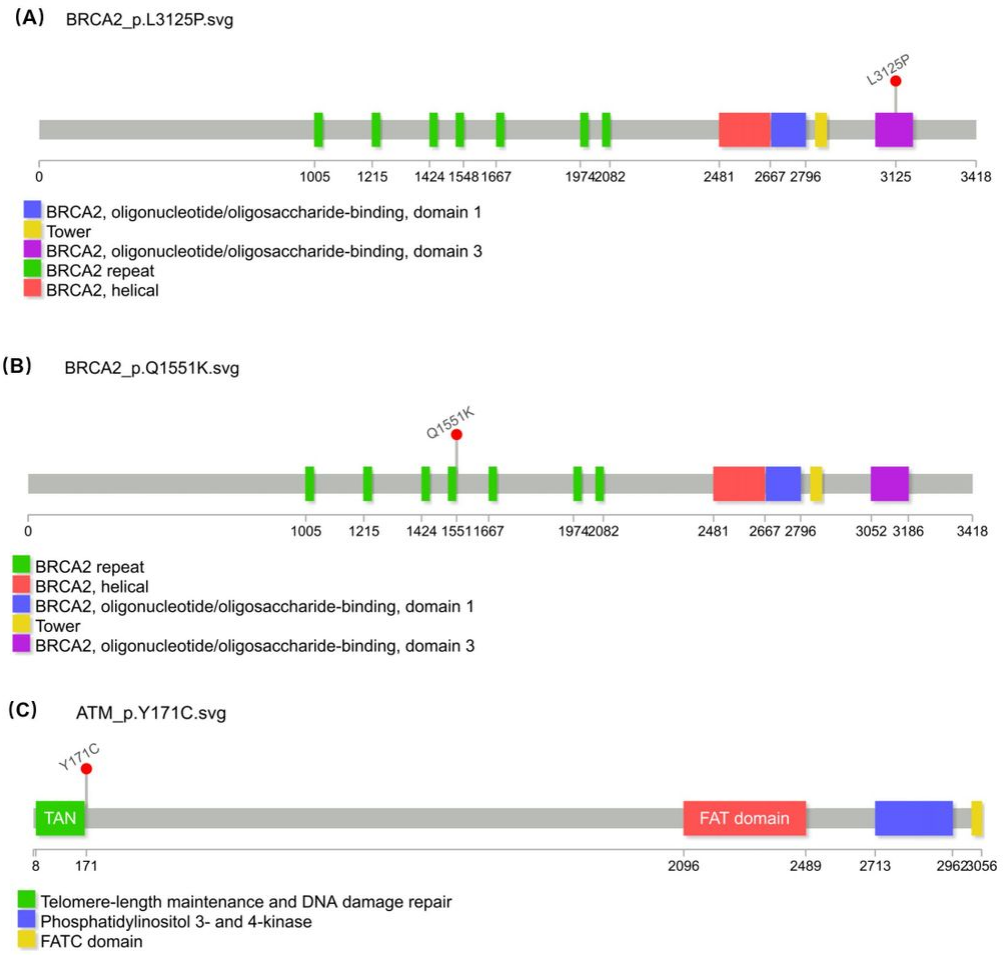

Figure 3. A &B) Mutations plots in BRCA2 gene C) Mutation plots in ATM genes. The plots were generated using the online tool Mutation Mapper

Figure 3

Please See image above for figure legend.