Cancer Management and Research

Elevate Series

Open Access Full Text Article

REVIEW

Integrating PARP Inhibitors in mCRPC Therapy: Current Strategies and Emerging Trends

Bicky Thapa[1,*], Navonil De Sarkar[2–4,*], Subhajit Giri[2,3], Komal Sharma[2–4], Mingee Kim[5], Deepak Kilari[1]

[1]Division of Hematology and Oncology, Medical College of Wisconsin, Milwaukee, WI, USA; [2]Medical College of Wisconsin Cancer Center, Milwaukee, WI, USA; [3]Department of Pathology, Medical College of Wisconsin, Milwaukee, WI, USA; [4]Data Science Institute, Medical College of Wisconsin, Milwaukee, WI, USA; [5]School of Medicine, Medical College of Wisconsin, Milwaukee, WI, USA

*These authors Contributed equally to this work

Correspondence: Deepak Kilari, Email dkilari@mcw.edu

Abstract: Metastatic castrate-resistant prostate cancer (mCRPC) is associated with poor prognosis. DNA damage response (DDR) genes are commonly altered in mCRPC rendering them as promising therapeutic targets. Poly (ADP ribose) polymerase inhibitors (PARPi) demonstrated antitumor activity in mCRPC patients with DDR gene mutations through synthetic lethality. Multiple clinical trials with PARPi monotherapy exhibited encouraging clinical outcomes in selected patients with mCRPC. More recently, three Phase III randomized clinical trials (RCTs) combining PARPi with androgen receptor signaling inhibitors (ARSIs) demonstrated improved antitumor activity compared to ARSI monotherapy in mCRPC patients as the first-line therapy. Clinical benefit was more pronounced in patients harboring DDR alterations, specifically *BRCA1/2*. Interestingly, antitumor activity was also observed irrespective of DDR gene mutations, highlighting BRCAness phenotype with androgen receptor blockade resulting in synergistic activity between ARSIs and PARPi. In this review, we discuss the clinical efficacy and safety data of the combination of PARPi plus ARSI in all Phase 3 randomized controlled trials (RCTs), emphasizing strategies for patient selection and highlighting emerging trends based on clinical trial data.

Keywords: PARP inhibitors, talazoparib, ARSI, DDR genes, HRD, metastatic CRPC

Introduction

Prostate cancer has become the leading cancer diagnosis among American men in 2024, with a staggering 299,010 new cases estimated, highlighting a critical public health challenge.[1] The management of prostate cancer has long centered around targeting the androgen receptor (AR).[2] Nevertheless, the formidable challenge arises as alterations within the AR signaling pathway provoke resistance, propelling the progression to castration-resistant prostate cancer (CRPC).[2,3] Historically, patients with metastatic CRPC (mCRPC) had limited therapeutic options and poor prognoses. Despite notable recent strides in therapeutic innovation, the five-year relative survival rate for metastatic prostate cancer hovers at a mere 34%.[4] A recent Swedish population-based study has further underscored the gravity of the situation, reporting a median overall survival of a mere 1.86 years for individuals with CRPC, irrespective of metastatic status.[5]

Docetaxel is one of the preferred choices of treatment for chemotherapy-naïve mCRPC based on the findings from SWOG 99–16, and the TAX327 trial.[6,7] Subsequently, 2nd-generation androgen receptor signaling inhibitors (ARSIs) such as abiraterone, apalutamide, and enzalutamide have demonstrated improved clinical outcomes as 1st line systemic treatment. However, there has been no direct comparative trial conducted between ARSIs and chemotherapy. Although these advancements heralded improved outcomes, the median radiographic progression-free survival (PFS) with first-line ARSI plateaued at around 20 months. Additionally, the limited benefit observed upon switching ARSIs upon progression accentuates the pressing need for novel and more effective therapeutic regimens in the pre-chemotherapy setting.[8–12] Aside from docetaxel and ARSIs, there are additional approved first-line treatments for a specific subset of mCRPC patients. These include PARP inhibitors in combination with ARSI, pembrolizumab for patients with microsatellite instability-high status (MSI-high), sipuleucel-T, and Radium-223 for those with symptomatic bony metastases.

Received: 20 April 2024
Accepted: 16 August 2024
Published: 17 September 2024

Genomic profiling studies demonstrated notable heterogeneity in the genomic alterations in the different stages of prostate cancer. For example, mCRPC patients often have genomic alterations in *AR, TP53*, and *RB1* compared to localized prostate cancer. Specific alterations such as TMPRSS2-ERG fusions, and changes in PTEN, SPOP, and FOXA1, mark distinct subtypes, including those related to DNA damage repair (DDR).[13–17] Pritchard et al reported germline DDR mutations in 4.6% of localized prostate cancer, with more than twofold increase in mCRPC (11.8%).[18] The Cancer Genome Atlas (TCGA) study reported DDR gene aberrations in 19% of localized cases,[19] while a similar mCRPC focused study showed aberrations in 23% of the case series (SU2C east coast dream team study).[13] These prevalence statistics are supported by extensive molecular profiling on localized, oligometastatic, and mCRPC case series.[14,20–25] Notably, disruptions in homologous recombination-mediated repair (HRR) pathways have garnered significant interest due to their susceptibility to poly-(ADP ribose) polymerase (PARP) inhibitors (PARPi) via synthetic lethality mechanisms.[26–28] Encouragingly, multiple randomized clinical trials have showcased the promising clinical efficacy of PARP inhibitor monotherapy in mCRPC patients. These findings underscore the potential of targeting DDR gene aberrations, particularly through PARP inhibition, in the therapeutic landscape of advanced prostate cancer.

Within the landscape of prostate cancer, the Androgen Receptor (AR) gene and its aberrant signaling pathways play a crucial role, shaping the trajectory of disease progression. Notably, a body of prior research has underscored the intricate relationship between AR signaling and the expression of various genes within the DNA damage repair (DDR) pathway.[29] Preclinical investigations have shed light on the phenomenon wherein the suppression of the Homologous Recombination Repair (HRR) pathway, triggered by Androgen Deprivation Therapies (ADT), instigates heightened activity of Poly-(ADP ribose) polymerase (PARP), indicative of a nuanced interplay between AR pathways and DDR genes.[30] These intriguing insights hint at the potential induction of BRCAness, offering a compelling rationale for exploring synthetic lethality through combined inhibition of Androgen Receptor Signaling and PARP. Noteworthy clinical trials have recently demonstrated promising responses to such combination therapies, even among metastatic castration-resistant prostate cancer (mCRPC) patients lacking specific DDR gene alterations.

This review examines key clinical trial outcomes to understand the clinical significance of PARP inhibitor monotherapy and combination therapies with AR signaling inhibitors (ARSI), emphasizing patient stratification and outcomes.

Therapeutic Implications of Dysfunctional DNA Damage Response Pathways

Cancer cells deploy sophisticated DNA repair strategies to sustain cellular balance, with critical pathways addressing single- and double-strand DNA breaks to prevent malignancy. PARP proteins, particularly PARP1, are crucial for DNA repair and have important implications for treatment. Using PARP inhibitors (PARPi) for cancers that lack the HRR mechanism could be of significance in treating mCRPC patients, as a substantial number of patients can have genomic aberrations in DNA repair genes. Comprehensive genomic profiling facilitates treatment personalization, a concept supported by the National Comprehensive Cancer Network (NCCN), marking a transition to precision oncology designed to improve patient outcomes. In breast and ovarian cancers with *BRCA1/2* mutations, platinum-based chemotherapy improves survival. Although not standard for mCRPC, retrospective studies indicate patients with DDR gene alterations may benefit from platinum chemotherapy, pending validation from prospective studies.

Poly(ADP-Ribose) Polymerase Inhibitors and Synthetic Lethality

Poly(ADP-ribose) polymerase inhibitors (PARPi) are stratified into categories based on their potential to induce allosteric changes in target proteins. There are three types: Type I inhibitors such as EB-47 that mimic benzamide adenine dinucleotide; Type II inhibitors, including talazoparib and olaparib; and Type III inhibitors, such as niraparib, rucaparib, and veliparib.[31]

At present, the US Food and Drug Administration (FDA) has approved four PARPi for metastatic castration-resistant prostate cancer (mCRPC): rucaparib, niraparib, olaparib, and talazoparib. Of importance, talazoparib and olaparib exhibit a moderate increase in DNA binding affinity without affecting the allosteric sites of PARP1. Preclinical studies have shown that the cytotoxicity of PARPi correlates with their PARP trapping efficacy, with talazoparib emerging as the most potent trapper followed by olaparib among the evaluated PARPi.[32–34] Rucaparib and niraparib, while effective catalytic inhibitors of PARP1, do not trap as efficiently as talazoparib.[32–34] The first in

human, Phase 1 clinical trial with olaparib in advanced solid tumors with germline *BRCA1/2* mutations exhibited anti-tumor activity with durable responses, especially in a patient with *BRCA2*-mutated CRPC.[35] Subsequently, phase 1 studies in molecularly selected advanced prostate cancer with germline *BRCA1/2* mutation PARPi (olaparib, talazoparib) showed anti-tumor activity.[36,37]

PARPi Monotherapy Clinical Trials in mCRPC

Several clinical trials have explored the efficacy and safety of PARP inhibitors as monotherapy in mCRPC patients with DNA repair gene alterations. The TOPARP-A (NCT01682772) and TOPARP-B (NCT01682772) trials evaluated olaparib, which showed promising results in mCRPC patients with DDR gene alterations, particularly in those with *BRCA1/2* mutations.[38,39] These trials demonstrated improved radiologic progression-free survival (rPFS) and overall survival (OS) in biomarker-positive patients compared to biomarker-negative patients (median 9.8 months vs 2.7 months; $p<0.001$). However, dose-dependent toxicities, such as anemia, were observed, necessitating dosage adjustments.[38] Similarly, the PROfound (NCT02987543) trial confirmed the efficacy of olaparib in mCRPC patients with DDR gene alterations, leading to its FDA approval in May 2020.[40] Patients were assigned to cohort A based on the presence of DDR alterations in *BRCA1, BRCA2*, or *ATM*, while those with other DDR genes (*BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD54L*) were enrolled in cohort B. Notably, olaparib significantly prolonged PFS (median 7.4 months vs 3.6 months; $p<0.001$) and OS (median 18.5 months vs 15.1 months; $p=0.02$) in cohort A when compared to standard treatments like enzalutamide or abiraterone.

In the TRITON2 (NCT02952534) trial, rucaparib was evaluated in *BRCA*-altered mCRPC patients, showcasing an overall response rate (ORR) of 43.5% (95% CI, 31.0%–56.7%) and a prostate-specific antigen (PSA) response in 54.8% of patients.[41] This led to the FDA's accelerated approval of rucaparib for *BRCA*-altered mCRPC patients. In addition, this study explored rucaparib's efficacy in non-BRCA mutated DDR genes. While responses were limited in patients with *ATM, CDK12*, and *CHEK2* alterations, promising anti-tumor activity was reported in other DDR gene cohorts, including *PALB2, FANCA, BRIP1*, and *RAD51B*. The study reported manageable adverse events, predominantly myelosuppression. Subsequently, a phase 3 randomized study, TRITON3 (NCT02975934) evaluated the efficacy of rucaparib in mCRPC patients with *BRCA1/2* and *ATM* alterations.[42] In this study, rucaparib was compared with the control group, which is the physician's choice of treatment, ie, 2nd generation ARSIs or docetaxel. Rucaparib demonstrated significant improvement in imaging-based PFS in the BRCA subgroup with a median PFS of 11.2 months vs 6.4 months as compared to the control group with HR of 0.50 (95% CI, 0.36–0.69; $p<0.001$ by og rank test). Similarly, PFS was longer in intention to treat population, median PFS of 10.2 months in the rucaparib arm vs 6.4 months in the control group; HR of 0.61 (95% CI, 0.47–0.80, $p<0.001$ by log rank test). No significant difference in PFS was observed in the ATM subgroup. Likewise, the GALAHAD (NCT02854436) trial, which was the first to assess the efficacy of niraparib in heavily pretreated mCRPC, demonstrated its activity in *BRCA*-altered mCRPC patients.[43] The study found a significant ORR of 34.2% (26 of 76 patients) in the BRCA cohort and 10.6% (5 of 47 patients) in the non-BRCA group, with rPFS of 8.08 months and 9.93 months in the respective cohorts. The most common adverse events observed with niraparib included nausea, anemia, and vomiting.

Talazoparib, another potent PARP inhibitor, exhibited significant anti-tumor activity in heavily pretreated mCRPC patients with DDR gene mutations in the TALAPRO-1 (NCT03148795) trial.[44] Both BRCA1/2 and non-BRCA mutated cohorts showed favorable response rates, with an rPFS of 5.6 months (95% CI, 3.7–8.8) in the overall cohort and 11.2 months (95% CI 7.5–19.2) in the BRCA1/2 cohort. Notably, the study found no difference in clinical outcomes between germline and somatic DDR gene alterations. Common adverse events included anemia, nausea, decreased appetite, and asthenia. Overall, these trials highlight the evolving landscape of targeted therapy in mCRPC and the potential of PARP inhibitors for patients with specific DDR gene alterations. Table 1 summarizes the clinical outcome of PARPi monotherapy in mCRPC.

Table 1 Summary of Phase II and III Clinical Trials in mCRPC Patients with PARPi Monotherapy. Table summarizing results from 7 landmark PARPi monotherapy trials. All trials led one common inference that patients with BRCA loss yielded highest measurable response

Clinical Trials	Study Design	PARPi	Patient Selection	Total Patients Enrolled	DDR Gene Alterations	Clinical Outcome	Reported Grade 3 Adverse Events
TOPARP-A (2015)[39]	Phase-II, Open label	Olaparib	Molecularly unselected mCRPC; prior exposure to ARSI/ chemotherapy.	n=50	33% with DDR gene alterations (DDR+); *BRCA2* (14%), *ATM* (10%)	rPFS: DDR (+) vs DDR (−): median 9.8 mo vs 2.7 mo; p<0.001. OS: DDR (+) vs DDR(–): median (13.8 mo vs 7.5 mo; p=0.05. 6% DDR (–) attained objective response.	Anemia: 20%. Fatigue: 12%. Leucopenia: 6%. Thrombocytopenia: 4%. Neutropenia (4%)
TOPARP-B (2020)[38]	Phase-II, open-label, RCT	Olaparib	mCRPC, DDR gene alterations[$]; taxane-treatment history (+); ARSI exposure agnostic	N=98 (2 treatment groups. Group 1: n=49 Olaparib 300 mg twice daily; Group 2, n=49, Olaparib 400 mg twice daily).	*BRCA1/2* (33%) *ATM* (21%), *CDK12* (21%), *PALB2* (7%)	ORR- 400 mg treatment arm: 54%; 300 mg treatment arm; 39%. ORR- B*RCA1/2* mutant: 83%, 57% *PALB2* mutant: 57% and ATM mutant: 37%.	300 mg cohort Anemia: 31%. 400 mg cohort Anemia: 37%
PROfound (2020)[40]	Phase III, RCT	Olaparib	Predefined DDR gene altered mCRPC[#]; Progressed on ARSI; chemo naïve	Cohort A n=245, Cohort B n=142	Cohort A (n=245) with *BRCA1/2* or *ATM* alterations. Cohort B (n=142) with at least one of the other 12 prespecified DDR gene alterations	Cohort A- Median rPFS 7.4 vs 3.6 mo, P<0.001. Overall population (Cohorts A & B) median rPFS 5.8 vs 3.5 mo, P<0.001	Olaparib arm Anemia: 21%. Placebo arm Anemia: 5%
TRITON3 (2023)[42]	Phase-III, RCT	Rucaparib	mCRPC with *BRCA1/2* and *ATM* alterations. Prior ARSI exposure	Rucaparib arm n=270, Control arm n=135	BRCA1/2 (n=302). ATM (n=103)	BRCA subgroup- median PFS of 11.2 mo (rucaparib arm) vs 6.4 mo (control arm), p<0.001 by long-rank test. ORR of 45% vs 17%	Anemia (24%). Neutropenia (7%)
TRITON2 (2020)[41]	Phase-II, open level	Rucaparib	mCRPC Prior ARSI exposure.	n=115	*BRCA1* (n=13) *BRCA2* (n=102)	ORR -Cohort with measurable disease: 44%. Entire cohort PSA response: 55%	Anemia: 25%
GALAHAD (2022)[43]	Phase-II, open label	Niraparib	mCRPC with prespecified DDR gene alterations[^]	n=223; DDR mutants. *BRCA1/2* cohort (n=142). Non-*BRCA* cohort (n=81)	*BRCA1/2* mutants with measurable disease (n=76). *BRCA* intact with measurable disease (n=47)	ORR- *BRCA mutant* cohort: 34%. *BRCA* intact cohort: 11%	Anemia: 33%. Thrombocytopenia: 16%. Neutropenia: 10%
TALAPRO-1 (2021)[44]	Phase II, open label	Talazoparib	mCRPC, 11 predefined DDR gene alterations[##]	n=104	BRCA2 mutants (50%), BRCA1 mutants (4%), ATM mutants (14%) or PALB2 mutants (4%)	ORR-Overall cohort: 30%. *BRCA1/2* cohort: 46%	Anemia: 31%. Thrombocytopenia: 9% Neutropenia: 8%

Notes: [#]*BRCA1/2, ATM, BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD54;* [$]*BRCA1/2, ATM, PALB2, CDK12 and any other DDR gene.* [##]*BRCA1/2, ATM, ATR, CHEK2, FANCA, MLH1, MRE11A, RAD51C, PALB2*, and *NBN.* [^]*ATM, BRCA1/2, BRIP1, CHEK2, FANCA, HDAC2, PALB2.*

Abbreviations: ARSIs, Androgen receptor signaling inhibitors; DDR, DNA damage response; mCRPC, Metastatic castration-resistant prostate cancer; mo, Month; ORR, Objective response rate; OS, Overall survival; RCT, Randomized controlled trial; rPFS, radiographic progression free survival.

PARPi and ARSI in mCRPC and Its Clinical Outcome

Preclinical studies have demonstrated a synergistic effect between androgen receptor signaling inhibitors (ARSI) and poly(ADP-ribose) polymerase inhibitors (PARPi). There are claims that blocking the androgen receptor may enhance sensitivity to PARPi by inducing a BRCAness phenotype.[45,46] Based on this concept, the Phase 2 randomized clinical trial was conducted to evaluate the efficacy and tolerability of olaparib in combination with abiraterone (NCT01972217).[47] In this study, metastatic CRPC patients were enrolled regardless of HRR genomic alteration status. Of the 142 eligible mCRPC patients, 71 randomized to olaparib plus abiraterone and the other 71 patients to placebo and abiraterone. The median radiographic progression-free survival (rPFS) was significantly higher in olaparib arm; 13.8 months as compared to 8.2 months in the placebo arm; hazard ratio (HR) 0.65, [95% CI 0.44–0.97; P=0.034]. The encouraging preclinical and clinical outcome data with the combination therapy-led investigators to further evaluate the efficacy of PARPi and ARSI as 1st line combination therapy in phase 3 prospective randomized clinical trials. Tables 2–4 summarizes the patients selection criterion and clinical outcomes in mCRPC with combination therapy.

(i) **BRCAaway (NCT03012321, Phase 2, n=61):** The encouraging results from biomarker guided phase 2 clinical trial BRCAAway garnered attention at the recent ASCO GU 2024 event.[51] The study evaluated the efficacy of abiraterone/prednisone (Arm I) vs olaparib (Arm II) vs olaparib + abiraterone/prednisone (Arm III) in mCRPC patients with *BRCA1/2* or *ATM* alterations. A total of 61 patients were randomized to the 3 arms: Arm I (n=19), Arm II (n=21), and Arm III (n=21). The median PFS was 8.4 months in Arm I, 14 months in Arm II and 39 months in Arm III. The objective response rates observed in the trial were 29% for the combination of Olaparib and Abiraterone (Arm III), 9.5% for Olaparib alone (Arm II), and 21% for Abiraterone alone (Arm I). Despite being a study with a small cohort of patients, the combination of olaparib with abiraterone/prednisone showed promising clinical efficacy, resulting in an extended progression-free survival (PFS) in mCRPC patients with *BRCA1/2* or *ATM* mutations.

(ii) **MAGNITUDE (NCT03748641, Phase 3 randomized study, n=423):** The randomized clinical trial investigated the efficacy of combining niraparib with abiraterone and prednisone (Abi/Pred) versus a placebo with Abi/Pred in the management of patients with mCRPC in a first-line treatment setting.[50] The trial's inclusion criteria mandated patients to be at least 18 years of age with a confirmed mCRPC diagnosis defined by homologous recombination repair (HRR) gene alteration status. A panel of nine predefined genes (*BRCA1/2, ATM, BRIP1, CDK12, CHEK2, FANCA, HDAC2, PALB2*) were scrutinized for mutations. Exclusion criteria encompassed patients who previously received systemic therapies such as ARSI (enzalutamide, apalutamide, darolutamide) or docetaxel in a castration-resistant context. Nonetheless, systemic therapies for non-metastatic and metastatic castrate-sensitive scenarios did not preclude study participation. Prior to randomization, enrolled subjects were permitted up to four months of Abi/Pred therapy for mCRPC. Subjects were stratified into two cohorts based on HRR mutation status (HRR deficient or HRRd and HRR efficient or non-HRRd) and were randomized in a 1:1 ratio to receive either the investigative combination of niraparib with Abi/Pred or the control regimen of placebo with Abi/Pred. Table 2 summarizes the patient's selection criteria.

The study's primary endpoint was radiographic progression-free survival (rPFS). Secondary endpoints included time to initiation of cytotoxic chemotherapy (TCC), time to prostate-specific antigen (PSA) progression (TPP), objective response rate (ORR), and patient reported outcomes (PRO). In this study, the functional assessment of cancer therapy-prostate (FACT-P) total score was employed to assess the patient-reported quality of life changes (Table 4).

A total of 423 patients were enrolled in the HRRd cohort, and 233 patients were in the non-HRRd cohort. In the HRRd cohort, 212 were randomized to the niraparib + Abi/Pred arm, and 211 were assigned to the Abi/Pred + Placebo arm. In the HRRd cohort, niraparib + Abi/Pred improved rPFS compared to the placebo group (16.5 vs 13.7 months); HR 0.73 (95% CI, 0.56–0.96; P=0.022). In subgroup analysis in patients with *BRCA1/2* alterations, median rPFS was significantly longer in the intervention arm, 16.6 vs 10.9 months in the placebo arm; HR 0.53 (95% CI, 0.36–0.79; P=0.001). In the non-HRRd cohort (n=233), 117 were assigned to niraparib + Abi/Pred and 116 to placebo + Abi/Pred. The evaluation in the non-HRR cohort revealed no therapeutic advantage with niraparib, as indicated by the lack of improvement in rPFS and/or time to PSA progression, with an HR of 1.09 (95% CI, 0.75–1.57; P=0.66). Subsequently, the non-HRR cohort was stopped prematurely after meeting a pre-defined futility endpoint. OS data were immature at the time of primary data analysis. Table 3 summarizes the clinical outcomes. In HRRd cohort, niraparib + Abi/pred showed clinical benefits with delay in TCC, TPP, and TSP (highlighted in Table 4). Anemia and hypertension

Table 2 Summary of Patient Selection Criterion in Phase 3 Clinical Trials

Phase III Clinical Trials	TALAPRO-2[48] (NCT03395197)	PROpel Study[49] (NCT03732820)	MAGNITUDE[50] (NCT03748641)
Sample size	Total: 805, Tala + Enza (n=402), Placebo + Enza (n=403)	Total: 796, Olaparib + Abi/Pred (n=399), Placebo + Abi/Pred (n=397)	Total: 423, Niraparib + Abi/pred (n=212), Placebo + Abi/Pred (n=211)
Median Age (Years)	Talazo arm (71 yrs), Placebo arm (71yrs)	Olaparib arm (69 yrs), Placebo arm (70 yrs)	Niraparib arm (69 yrs), Placebo arm (69 yrs)
Race distribution (%)	Talazo arm: White (60%), Asian (32%), AA (3%), Placebo arm: White (63%), Asian (30%), AA (1%)	Olaparib arm: White (71%), Asian (17%), AA (4%), Placebo arm: White (69%), Asian (18%), AA (3%)	Entire cohort: White (74%), Asian (17%), AA (1%)
Treatment cohorts	Talazo arm vs Placebo arm	Olaparib arm vs Placebo arm	Niraparib arm vs Placebo arm
Disease site	Talazo arm: Bone (87%), Visceral (14%), Placebo arm: Bone (85%), Visceral (19%)	Olaparib arm: Bone (88%), Visceral (13%), Placebo arm: Bone (85%), Visceral (13%)	Niraparib arm: Bone (86%), Visceral (24%), Placebo arm: Bone (81%), Visceral (19%)
Biomarker selected enrollment	No	No	Yes
HRRd gene set pool	$12 HRR gene panel	#14 HRR gene panel	^9 HRR gene panel
HRR gene aberration frequency (%)	Talazo arm (21%), Placebo arm (21%)	Olaparib arm (28%), Placebo arm (29.0%)	24.9% pts undergone HRR gene status prescreening, Patients with HRRd randomized to niraparib and placebo arm.
BRCA1/2 loss (%)	Talazo arm 7% and Placebo arm (8%)	*BRCA1*: Olaparib arm (2%), placebo arm (1%), *BRCA2*: Olaparib arm (9.5%), placebo arm (8.8%)	Niraparib arm: *BRCA1* (6%), *BRCA2* (41%), Placebo arm: *BRCA1* (2%), *BRCA2* (42%)
Prior abiraterone or enzalutamide (%)	Talazo arm (6%), Placebo arm (7%)	*Olaparib arm (1%), *Placebo arm (0%)	@Niraparib arm (24%), @Placebo arm (23%)
Prior docetaxel for mCSPC	Talazo arm (21%), Placebo arm (23%)	Olaparib arm (23%), Placebo arm (22%)	Niraparib arm (19%), Placebo arm (21%)

Notes: $*BRCA1/2, PALB2, ATM, ATR, CHEK2, FANCA, RAD51C, NBN, MLH1, MRE11A, CDK12*. #*BRCA1/2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L*. ^*BRCA1/2, ATM, BRIP1, CDK12, CHEK2, FANCA, HDAC2, PALB2*. @ ARSI received Up to 4 months prior to randomization for mCRPC. *The trial excluded patients who received prior treatment with abiraterone and prednisone. Second-generation ARSIs in the CSPC setting were permitted, given that no disease progression occurred during and immediately after treatment.

Abbreviations: AA, African American; Abi/Pred, Abiraterone and Prednisone; Enza, Enzalutamide; HRRd, Homologous recombination repair gene mutation; mCSPC, Metastatic castrate sensitive prostate cancer; Tala, Talazoparib.

Table 3 Summary of Clinical Outcomes (Primary Endpoints) in Phase 3 Randomized Clinical Trials Evaluating Efficacy of PARPi and ARSI combinations in mCRPC Patients in 1st Line Treatment Setting

Phase III Clinical Trials	TALAPRO-2[48] (NCT03395197)	PROpel Study[49] (NCT03732820)	MAGNITUDE[50] (NCT03748641)
Primary endpoint (rPFS)	**HRRd unselected cohort** Talazo arm: Median PFS Not reached. Placebo arm: Median PFS 22 mo. HR 0.63 (95% CI, 0.51–0.78; p<0.0001) ***HRRd subgroup*** Talazo arm: Median PFS 28 mo. Placebo arm: Median PFS 16 mo. HR 0.46 (95% CI, 0.30–0.70; p=0.0003) ***Non-HRRd subgroup*** Talazo arm: Median PFS not reached. Placebo arm: Median PFS 23 mo. HR of 0·70 (0.54–0.89; p=0.0039)	Median rPFS 24.8 months (Olaparib arm) vs 16.6 (placebo arm); HR 0.66 (95% CI, 0.54–0.81; p<0.001)	In overall HRRd cohort, rPFS 16.5 vs 13.7, HR 0.73 (95% CI, 0.56–0.96; P=0.022); Non-HRRm cohort HR of 1.09 (95% CI, 0.75–1.57; P=0.66)

(*Continued*)

Table 3 (Continued).

Phase III Clinical Trials	TALAPRO-2[48] (NCT03395197)	PROpel Study[49] (NCT03732820)	MAGNITUDE[50] (NCT03748641)
Outcome in pts with *BRCA1/2* alterations	HR for rPFS was 0.23 (95% CI, 0.10–0.53; p=0.0002)	NR	Median rPFS in the *BRCA1/2* 16.6 mo (Niraparib arm) vs 10.9 mo (Placebo arm), HR 0.53 (95% CI, 0.36–0.79; P=0.001)
Outcome in non-*BRCA1/2* alterations	HR for rPFS was 0.66 (95% CI, 0.39–1.12, P=0.12)	NR	HR 0.99 (95% CI, 0.68–1.44) in subgroup with non-BRCA for rPFS

Abbreviations: CI, Confidence interval; HRRd, Homologous recombination repair gene mutation; mo, months; HR, Hazard Ratio; rPFS, Radiographic progression free survival; Tala, Talazoparib.

Table 4 Summary of Secondary or Other Exploratory End Points and Patient Safety Data

Phase III Clinical Trials	TALAPRO-2[48] (NCT03395197)	PROpel Study[49] (NCT03732820)	MAGNITUDE[50] (NCT03748641)
ORR	**Entire cohort** Talazo arm (n=120): ORR 62% (CR 45, PR 29). Placebo arm (n=132): ORR 44% (CR 24, PR 34) ***HRRd subgroup*** Talazo arm (n=33): ORR 79% (CR 19, PR 7). Placebo arm (n=26); ORR 46% (CR 5, PR 7) ***Non-HRRd subgroup*** Talazo arm (n=87): ORR 55% (CR 26, PR 22). Placebo arm (n=106): ORR 43% (CR 19, PR 27)	Olaparib arm (n=161): ORR 58% (CR 7, PR 87). Placebo arm (n=160): ORR 48% (CR 10, PR 67). OR, 1.60, 95% CI 1.02–2.53	Niraparib arm (n=92): ORR of 60% (CR 20, PR 35). Placebo arm (n=82): ORR of 28% (CR 9, PR 14). RR, 2.13 (1.45–3.13); P<0.001
TCC/Time to subsequent therapy or death	Talazo arm: Not reached. Placebo arm: Not reached. HR of 049 (95% CI, 0.28–0.65; P<0.0001)	Olaparib arm: 25 mo, Placebo arm: 20 mo, HR of 0.74(95% CI, 0.61–0.90)	Niraparib arm: NE. Olaparib arm: 26 mo. HR of 0.59 (95% CI, 0.39–0.89; P=0.011)
TSP	Talazo arm: Not reached. Placebo arm: Not reached	NR	Niraparib arm: NE. Olaparib arm: NE. HR 0.69; (95% CI, 0.47–0.99; P=0.04)
TPP	Talazo arm: 27 mo. Placebo arm: 18 mo. HR 0.72; (95% CI, 0.58–0.89; P=0.0020)	Olaparib arm: NR. Placebo arm: 12 mo. HR 0.55; (95% CI, 0.45–0.68)	Niraparib arm: 18.5 mo. Placebo arm: 9.3 mo. HR 0.57; (95% CI, 0.43–0.76; P<0.001)
PRO	TTD in GHS/QoL longer in Talazo arm. GHS/QoL favored placebo arm	Least-square mean change from baseline FACT-P total score. Olaparib arm: −4.85. Placebo arm: −4.03	FACT-P total scores for QoL were similar in both arms
Safety, incidence of any grade ≥3 TEAEs	Talazo arm (59%). Placebo arm (18%)	Olaparib arm (47%). Placebo arm (38%)	Niraparib arm (67%). Placebo arm (46%)
Dose reductions due to TEAEs	Talazo arm: Tala (53%), Enza (15%). Placebo arm: Placebo (7%), Enza (8%)	Olaparib arm: Olaparib (20%), Abi (3%). Placebo arm: Placebo (6%), Abi (9%)	Niraparib arm: Niraparib (20%), Abi (3%), Prednisone (9%). Placebo arm: Placebo (3%), Abi (3%), Prednisone (6%)
Dose discontinuation due to TEAEs	Talazo arm: Tala (19%), Enza (11%). Placebo arm: Placebo (12%), Enza (11%).	Olaparib arm: Olaparib (14%), Abi (9%). Placebo arm: Placebo (8%), Abi (9%).	Niraparib arm: Niraparib (11%), Abi (9%), Prednisone (9%). Placebo arm: Placebo (6%), Abi (6%), Prednisone (5%).

(*Continued*)

Table 4 (Continued).

Phase III Clinical Trials	TALAPRO-2[48] (NCT03395197)	PROpel Study[49] (NCT03732820)	MAGNITUDE[50] (NCT03748641)
Common toxicities, grade 3/4	Talazo arm: Anemia (46%), Neutropenia (18%), Thrombocytopenia (7%), HTN (5%). Placebo arm: Anemia (4%), Neutropenia (1%), Thrombocytopenia (1%), HTN (7%).	Olaparib arm: Anemia (15%), HTN (4%), PE (7%). Placebo arm: Anemia (3%), HTN (3%), PE (2%)	Niraparib arm: Anemia (28%), HTN (15%), Thrombocytopenia (7%), Neutropenia (7%). Placebo arm: Anemia (8%), HTN (12%), Thrombocytopenia (2%), Neutropenia (1%)
Current approval for clinical use	mCRPC with alterations in any of the 12 specified HRR genes[$]	mCRPC pts with *BRCA1/2* alterations	mCRPC pts with *BRCA1/2* alterations

Notes: [$]*BRCA1/2, PALB2, ATM, ATR, CHEK2, FANCA, RAD51C, NBN, MLH1, MRE11A, CDK12.*

Abbreviations: CI, Confidence interval; CR, Complete response; FACT-P, Functional Assessment of Cancer Therapy–Prostate; GHS/QoL, Global health status/quality of life; HR, Hazard ratio; HRR, Homologous recombination repair; HTN, Hypertension; mCRPC, Metastatic castration resistant prostate cancer; mo, Months; NE, Not evaluable; NR, Not reported; ORR, Objective response rate; PE, Pulmonary embolism; PR, Partial response; PRO, Patient reported outcomes; PSA, Prostate specific antigen; pts, Patients; QoL, Quality of life; OR, Odd ratio; rPFS, Radiographic progression free survival; RR, Relative risk; Tala, Talazoparib; TEAEs, Treatment-emergent adverse events; TCC, Time to initiation of cytotoxic chemotherapy; TPP, Time to PSA progression; TSP, Time to symptomatic progression; TTD, Time to definitive clinically meaningful deterioration.

were the most common grade ≥3 adverse events. Based on these data, the FDA approved niraparib + Abi/Pred as 1st line treatment for mCRPC patients with *BRCA1/2* alterations.

(iii) **PROpel (NCT03732820, Phase 3 double-blind randomized study, n=796):** The randomized trial evaluated the efficacy of Abi/Pred ± Olaparib in biomarker unselected (ie, irrespective of HRR status) mCRPC patients as 1st line treatment.[49] Metastatic CRPC patients (except for ADT) must be treatment-naive to be eligible for enrollment in the clinical trial. First-generation ARSI, such as bicalutamide, flutamide, and nilutamide, were permitted till four weeks prior to the randomization. Docetaxel in the setting of non-metastatic prostate cancer and mCSPC were allowed if there was no evidence of disease progression. Patients who received treatment with 2nd generation ARSIs (except for abiraterone) for mCSPC were eligible for the study if no disease progression during treatment and systemic treatment was stopped 12 months before randomization. Table 2 outlines the patients selection criteria.

The pivotal study focused on rPFS as its primary endpoint, while secondary endpoints included time to subsequent anti-cancer therapy, pain progression, OS, and PRO, with ORR, disease control rate, PSA response, and TSP serving as exploratory objectives. Like MAGNITUTE trial, FACT-P total score was utilized to understand the how patients reported changes in their quality of life (Table 4). Investigators pre-specified a comprehensive panel of HRR genes for enrolling 796 patients, leading to 399 assigned to the olaparib arm and 397 to placebo. Within the cohort, 28.4% had HRR alterations. Notably, the median rPFS was significantly longer in the olaparib plus Abi-Pred group at 24.8 months compared to 16.6 months in the placebo arm, with a hazard ratio of 0.66 (95% CI, 0.54–0.81; P<0.001). The ORR in the olaparib arm was 58.4% compared to 48.1% in the placebo arm, with an odds ratio of 1.60 (95% CI, 1.02–2.53). The PSA50 response rate was higher in the olaparib arm at 79.3% versus 69.2% in the placebo. In patients with HRR alterations, the median rPFS was not reached in the olaparib arm, contrasting with 13.9 months in the placebo group (HR of 0.50, 95% CI 0.34–0.73). In the non-HRR-altered cohort, the median rPFS was 24.1 months for olaparib versus 19.0 months for placebo (HR of 0.76, 95% CI 0.60–0.97). Table 3 outlines the clinical outcome in this trial. The most prevalent treatment-emergent adverse events in the olaparib cohort included anemia, fatigue, and nausea (Table 4). The updated analysis of overall survival did not show a significant difference between the olaparib and placebo arms (HR of 0.81, 95% CI 0.67–1.00; P=0.054), yet the median OS in the olaparib group was 42.1 months compared to 34.7 months in the placebo group.[52] Table 4 summarizes the other exploratory endpoints. These findings underpinned the FDA's approval of olaparib in combination with Abi/Pred for the treatment of mCRPC patients with *BRCA1/2* alterations.[53]

(iv) **The TALAPRO-2 (NCT03395197, Phase 3 double-blind randomized; n=805):** This randomized, double-blind, placebo-controlled, phase 3 clinical trial evaluating the efficacy and safety of talazoparib plus enzalutamide vs placebo plus enzalutamide in the first-line setting with mCRPC.[48] Eligible mCRPC patients must be asymptomatic or minimally symptomatic at enrollment. Patients who received prior docetaxel and Abi/Pred or orteronel in the mCSPC setting were eligible for enrollment. However, patients were ineligible for enrollment if they received previous systemic

therapy for localized CRPC or mCRPC, except for ADT and first-generation ARSIs. Metastatic CRPC patients were excluded if prior treatment with 2nd generation ARSIs (enzalutamide, darolutamide, apalutamide, abiraterone), PARPi, cyclophosphamide, mitoxantrone, platinum-based chemotherapy within six months of randomization, and investigational drugs within four weeks of randomization. Table 2 summarizes the patient's selection criterion. The study enrolled mCRPC patients regardless of HRR alterations. Investigators prospectively assessed the 12 prespecified HRR gene alterations (*BRCA1/2, PALB2, ATM, ATR, CHEK2, FANCA, RAD51C, NBN, MLH1, MRE11A, CDK12*). The primary endpoint of the clinical trial was rPFS. Secondary endpoints were OS, ORR, PSA50 response, TPP, TCC, time to initiation of subsequent antineoplastic therapy, time to 1st skeletal events, time to disease progression or death, safety, and patient reported outcomes (PRO). In this study, PRO were analyzed using the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ-C30), Table 4. Eight hundred-five patients were enrolled in the study; 402 were randomly assigned to the talazoparib arm and 403 to the placebo arm. Talazoparib was dosed at 0.5 mg PO daily, and in patients with moderate renal impairment, 0.35 mg PO daily was the recommended dose, enzalutamide 160 mg PO daily. HRR gene alteration was noted in 21% (n=169) patients, and 79% (n=636) had no HRR gene alteration. *BRCA1/2* alteration was noted in 7% (n=27) patients in the talazoparib arm, and 8% (n=32) in the placebo arm. In the talazoparib arm, 21% (n=86) received prior docetaxel and 6% (n=23) received ARSI (abiraterone and orteronel) vs 23% (n=93) and 7% (n=27) in the placebo arm. Median rPFS was not reached for the talazoparib arm (95% CI, 27–5 months-not reached) vs 21.9 months (95% CI, 16.6–25.1) in the placebo arm. The HR for disease progression or death was 0.63 (95% CI, 0.51–0.78, P<0.0001). Talazoparib plus enzalutamide showed benefit in different subgroup; the risk of radiographic progression was 54% lower in HRR gene-altered patients with HR of 0.46 (95% CI, 0.30–0.70; P=0.0003) versus HR of 0.70 (0.54–0.89; P=0.0039) in non-HRR gene altered or unknown patients as compared to placebo group. Patients with *BRCA1/2* alteration garnered remarkably better rPFS with HR of 0.23 (95% CI, 0.10–0.53; P=0.0002) compared to the placebo arm. The non-BRCA1/2 altered group also demonstrated an improvement in rPFS with talazoparib HR of 0.66 (95% CI, 0.39–1.12, P=0.12). The clinical benefit was observed with talazoparib plus enzalutamide compared to the placebo arm irrespective of prior docetaxel in mCSPC setting, HR 0.56 (95% CI, 0.38–0.83, P=0.0038). Overall, clinical benefit was noted across all prespecified subgroups such as site of metastasis, HRR gene altered, non-HRR altered, *BRCA1/2* altered, non-BRCA1/2. Table 3 highlights the clinical outcome (primary end points) and Table 4 outlines the secondary or exploratory end points.

Biomarkers for PARP Inhibitor Sensitivity

Across all clinical trials, mCRPC with *BRCA1/2* alterations consistently demonstrated improvement in clinical outcomes with different PARPi (Table 1 and Table 3). Clinical benefits were noted irrespective of germline or somatic *BRCA* mutation. This is clinically important as approximately 10%–13% of mCRPC patients harbor *BRCA* alterations with the majority of patients with *BRCA2* mutations and only ~1–2% harboring *BRCA1*.[13,54–56] In the biomarker study from TOPARP-B trial, homozygous *BRCA2* deletions showed exceptional response with olaparib.[57] The authors also found that patients with loss of ATM expression in immunohistochemistry and biallelic PALB2 loss were associated with the clinical response with PARPi. The exploratory subgroup analysis from the phase III PROfound trial showed clinical benefit with olaparib in mCRPC patients with *BRCA* alterations.[58] In the BRCA2 cohort (n=128), the median PFS was 10.8 months in the olaparib arm vs 3.5 months in the control arm. On the other hand, in the BRCA1 cohort (n=13), the median PFS was 2.1 months vs 1.8 months. Particularly, prolonged clinical response with olaparib was observed in patients harboring *BRCA2* homozygous deletions (n=16) with the median rPFS of 16.6 months.[58] Beyond BRCAness, several genomic scores are now emerging to be strong predictors of PARPi response,[20,59–69] eg, the Homologous Recombination Deficiency (HRD) score, which integrates genomic scarring markers like loss of heterozygosity (LOH) and telomeric allelic imbalance (TAI), has been validated in various cancers to predict PARPi sensitivity.[69]

A retrospective multi-institutional study showed important clinical findings of differential clinical response with PARPi in mCRPC patients with *BRCA1* and *BRCA2* mutations.[70] Reduced efficacy was observed with PARPi in patients with *BRCA1* mutation as compared to *BRCA2*. In another retrospective study, PARPi demonstrated superior clinical activity in mCRPC patients harboring both *BRCA2* and *speckle-type POZ protein (SPOP)* mutation.[71]

A meta-analysis by Messina C et al reported the efficacy of combination treatment with PARPi plus ARPI from three-phase III RCTs (PROPEL, MAGNITUDE, and TALAPRO-2).[72] The clinical benefits of combination treatment were noted in 2 randomized clinical trials (RCTs) (PROPEL and TALAPRO-2) in molecularly unselected mCRPC patients, highlighting a synergy between ARSI and PARPi. The pooled analysis from 6 clinical trials, 4 RCTs (PROPEL, MAGNITUDE, TALAPRO-2, PROFOUND), and 2 single-arm clinical trials (TRITON-2, TALAPRO-1), revealed variable responses of PARP inhibitors across different DDR gene mutations.[73] The highest clinical benefit with PARPi was noted in mCRPC patients with *BRCA1/2*, *CDK12*, and *PALB2* mutations. No obvious benefit was observed in patients harboring *ATM* and *CHEK2* mutations. These insights are pivotal for advancing biomarker-driven patient selection and optimizing PARPi-based therapies, ultimately aiming to improve clinical outcomes for patients with HRR deficiencies.

CRPC Patient Selection for PARP Inhibitors in the Clinical Practice

PARP inhibitors are typically considered for mCRPC patients harboring DDR gene alterations such as *BRCA1/2*.[38–41,47,48,51,72,74–81] However, there are challenges in determining which PARP inhibitor to use in real-world practice, as improvement in clinical outcomes was demonstrated in multiple phase 3 clinical trials (both monotherapy and combination treatment).[47,48,81] In terms of monotherapy, PARP inhibitors (olaparib and rucaparib) monotherapy is the preferred choice in mCRPC patients harboring pathogenic *BRCA* mutation (germline or somatic) who progressed on ARSI agents. In addition, olaparib monotherapy can be considered in mCRPC patients harboring non-BRCA mutations (*ATM, BRIP1, BARD1, CHEK1, CHEK2, CDK12, FANCL, PALB2, RAD51B, RAD51C, RAD51D*, and *RAD54L*).

PARP inhibitors, in combination with ARSI, demonstrated improved clinical outcomes. However, no comparative trials have evaluated PARP monotherapy vs combination treatment. In context of treatment sequence, before the approval of combination therapy, ARSIs were used for treatment in the 1st line metastatic setting, with subsequent administration of PARP inhibitors following disease progression.

Data from PROPEL and TALAPRO-2 suggest benefit of combination treatment with PARPi and ARSI; however, olaparib and abiraterone is FDA approved for mCRPC patients with only *BRCA1/2* alterations. On the other hand, talazoparib and enzalutamide is FDA approved for mCRPC patients with any of the 12 HRR gene alterations, namely, *BRCA1/2, PALB2, ATM, ATR, CHEK2, FANCA, RAD51C, NBN, MLH1, MRE11A, and CDK12*. Talazoparib and enzalutamide showed rPFS benefits across all subgroups regardless of HRR gene status; however, maximum clinical benefits were observed in patients harboring *BRCA1/2* mutation; HR 0.23 (95% CI, 0.10–0.53, p=0.0002). The survival follow-up for this trial is ongoing, and currently, data is immature. The post-hoc exploratory analysis data from the TALAPRO-2 demonstrated improved rPFS with talazoparib plus enzalutamide in patients harboring *TMPRSS2-ERG* and *RB1* mutation.[82] The study suggested the possibility of synthetic lethality with PARPi via *TMPRSS-ERG* mediated repression of NHEJ.[82] Regarding safety profile, talazoparib plus enzalutamide was associated with grade≥3 adverse events in 75% of patients. The most common all cause adverse events were anemia, neutropenia, and fatigue. Therefore, safety considerations should be given to frail elderly patients who are susceptible to serious life-threatening side effects.

Based on the clinical trial data, all 3 combinations of PARP inhibitors with ARSI can be utilized as first-line systemic treatment. Picking one combination over others is a challenging decision as there is no head-to-head comparison of the trials. The overall survival data is either not yet available or remains immature, representing a notable limitation of the studies. In contrast to the BRCAAway study, the absence of crossover from the control group presents a challenge in assessing the relative efficacy of combination therapy vs sequential PARP inhibitor therapy. The studies also did not assess the correlation of clinical outcomes with other common somatic mutations such as AR alterations, tumor suppressor genes, and PI3K pathways in mCRPC, which are known to contribute to the aggressive nature of the disease.

PARP Inhibitors as Maintenance Therapy Agent in Advanced Cancer

PARP inhibitors (PARPi) have become crucial in the maintenance therapy landscape for patients with ovarian cancer, as evidenced by pivotal trials such as SOLO1 and OlympiAD.[83–85] These trials demonstrated that olaparib significantly extended progression-free survival (PFS) in ovarian and breast cancers with BRCA1/2 mutations, outperforming standard

therapeutic options. Specifically, in the SOLO1 trial, olaparib reduced the risk of disease progression or death by 70% compared to placebo.[83] This success has spurred further exploration of PARPi as maintenance therapy agents in various cancers, particularly for patients with defects in homologous recombination repair (HRR) mechanisms.

The PROfound trial's success led to the growing interest in using olaparib as a maintenance therapy agent in mCRPC patients, particularly with HRR gene alterations. This expansion has provided compelling data for personalized treatment strategies, emphasizing the need for continuous research to refine their application.[40] While PARPi have shown promise, determining optimal dosing schedules, whether continuous or intermittent, remains critical to balancing efficacy and minimizing toxicity. This underscores the need for further clinical research and real-world data to establish comprehensive guidelines for the use of PARPi in maintenance therapy for mCRPC.

Overcoming Challenges with PARP Inhibitors: Next-Generation Strategies and Innovations

Despite the promise of PARPi in treating mCRPC, several challenges limit their efficacy. Emerging evidence indicates that 40–50% of eligible mCRPC patients with HR mutations show limited or no response to PARPi, despite exhibiting HRD markers.[77,78] Resistance mechanisms, such as secondary mutations restoring HRR function, complicate treatment further.[78,86,87] Current genomic signatures like HRDetect and iHRD rely on accumulated genomic scars and lack real-time HRD detection sensitivity.[20,59] Additionally, systemic toxicity and poor tumor tissue accumulation hinder PARPi's bioavailability and efficacy. Another significant concern with the present generation of PARPi lies within a substantial fraction of patients who show grade 3 myelosuppression.[33,88–92] Next-generation PARPi aim to overcome these limitations through enhanced selectivity, potency, and bioavailability. Strategies include designing PARPi to counter resistance mechanisms, exploring combination therapies, and using liposomal formulations to improve tumor targeting and reduce toxicity.

Modulating the tumor microenvironment and using biomarker-driven patient selection with comprehensive panels and next-generation sequencing aim to better predict PARPi response. Combining PARPi with chemotherapy, radiation, immune checkpoint inhibitors, and targeted therapies is being evaluated to enhance efficacy and overcome resistance. These advancements promise to maximize PARPi's therapeutic potential, providing more effective treatment options for patients with HRR deficiencies and improving overall treatment outcomes in mCRPC.

Discussion

The advent of precision oncology has heralded a new era in the management of metastatic castration-resistant prostate cancer, shifting the therapeutic landscape towards more targeted interventions. Among these, PARPi have emerged as a pivotal therapy, especially for patients harboring DDR gene mutations. This review elucidates the significant strides made in understanding and treating mCRPC, underscoring the role of PARPi as a cornerstone of precision medicine in this context.

Lessons Learned from PARPi Monotherapies in the mCRPC Cohort

The clinical translation of PARPi for mCRPC management, particularly for tumors with DDR mutations, has been underpinned by robust clinical trials. Seminal studies such as TOPARP-A, PROfound, TRITON2, and GALAHAD have demonstrated the therapeutic potential of PARPi, with significant improvements in radiographic progression-free survival (rPFS) and, in some cases, overall survival (OS) among patients harboring specific DDR mutations.[39–41,43] The PROfound study,[40] which evaluated olaparib in mCRPC patients with alterations in DDR genes, underscored the clinical benefit of PARPi, showcasing a notable improvement in rPFS compared to standard-of-care treatments. Similarly, the TRITON2 trial[41] illustrated rucaparib's efficacy in mCRPC patients with *BRCA* mutations, reinforcing the premise that targeting DDR defects can elicit significant antitumor activity.

In a phase 3 randomized clinical trial, niraparib maintenance treatment in patient with platinum sensitive recurrent ovarian cancer showed clinical benefits regardless of HRD status.[93] Similarly, olaparib maintenance in germline *BRCA1/2* altered platinum sensitive metastatic pancreatic cancer demonstrated longer PFS.[94] With similar innovative idea,

a phase II, single arm clinical trial (NCT04288687) is ongoing to evaluate the clinical outcome of niraparib maintenance in platinum sensitive mCRPC patients harboring predefined somatic or germline DDR genes (*BRCA1/2, ATM, FANCA, CDK12, RAD51B, RAD54L, PALB2, CHEK2, HDAC2, or BRIP1*).[95]

Is the New Therapy Combination PARPi+ARSI a Leap Forward?

The interplay between DDR mechanisms and AR signaling pathways suggests a synergistic potential for combining PARPi with ARSI. Preclinical studies have revealed that AR signaling modulates the expression of genes involved in DDR, positing that AR inhibition could sensitize prostate cancer cells to PARPi.[45,46] Clinical investigations, such as the combination of talazoparib and Enzalutamide in the TALAPRO2 study,[40] have begun to explore this synergy, reporting enhanced clinical outcomes compared to either agent alone.

This combinatory approach heralds a promising avenue for mCRPC treatment, potentially overcoming resistance mechanisms to monotherapy and addressing a broader patient population. However, the intricacies of drug–drug interactions, optimal dosing strategies, and the identification of patients who would most benefit from such combinations necessitate further exploration. It is also essential to acknowledge that all three RCTs (TALAPRO-2, PROpel, and MAGNITUDE) testing efficacy of PARPi+ARSI had very distinctive clinical outcomes, possibly due to difference in study designs, patient selection criteria and most critically due to different characteristics of the respective PARPi. For example, enrolled mCRPC patients were allowed to have abiraterone plus prednisone up to 4 months before the randomization of mCRPC in the MAGNITUDE study, therefore about 1/3rd of the enrolled patients had ARSIs at the time of enrollment. Interestingly, these three clinical trials chose a distinctively different set of gene mutation status as the criterion to assign a patient HRRd status as well (Table 2). Conversely, the TALAPRO-2 study did not include mCRPC patients who had been treated with ARSIs within the six months prior to randomization. However, the study did permit the inclusion of patients who had previously been treated with docetaxel and abiraterone in the context of mCSPC. The PROpel study enrolled treatment-naïve mCRPC patients, and patients who received abiraterone in mCSPC setting were excluded from the study. Besides, patients on 2nd generation ARSIs except for abiraterone were eligible for the study if no disease progression and treatment was stopped 12 months before randomization. The PROpel and MAGNITUDE studies permitted the participation of individuals who had previously received docetaxel therapy, provided this treatment occurred before the progression to the metastatic castration-resistant prostate cancer (mCRPC) phase. Table 2 highlights the proportion of patients in all three RCTs who received systemic therapies before enrollment in the trial. Of importance, due to drug–drug interaction concerns the MAGNITUDE trial chose 200 mg once daily Niraparib dose in combination with abiraterone as compared to 300 mg once daily as monotherapy. With regard to toxicity, both olaparib and niraparib, in combination with abiraterone, had similar grade 3 and above toxicities when compared with monotherapy clinical trials (Table 1 and Table 4). However, talazoparib with enzalutamide was associated with significantly high grade ≥3 adverse events compared to monotherapy clinical trials. This underscores the need for more accurate patient selection criterion in the real-world setting for better clinical outcomes with manageable side effects with different PARPi. Currently, olaparib plus abiraterone and niraparib plus abiraterone are cleared by the FDA for mCRPC patients with *BRCA1/2* mutation, whereas talazoparib plus enzalutamide is FDA-approved for mCRPC patients with 12 DDR gene alterations as described above.

While the three phase 3 randomized trials focused on showing the efficacy of PARPi+ARSI against ARSI monotherapy as control arm; the relatively small-scale phase 2 study BRCAaway design convince us of the true essence of PARPi+ARSI treatment synergy.[51] The BRCAaway trial represents a significant leap forward, showcasing the potent synergy between Olaparib, a PARPi, and abiraterone, an ARSI, especially in patients harboring *BRCA1/2* or *ATM* mutations. The trial's design was meticulous, targeting a cohort of mCRPC patients with these specific genetic aberrations, which are known to compromise DNA damage response (DDR) mechanisms. The outcomes were compelling, with the combination therapy arm (Arm III) achieving a median progression-free survival (PFS) of 39 months, a remarkable improvement compared to monotherapy arms that are crossed over (ARSI monotherapy arm crossed over to a PARPi or vice versa).[51] Such statistical evidence underscores the trial's success, highlighting the critical role of PARPi +ARSI combination therapy synergy in treating patients with metastatic prostate cancer. Such an outstanding observation indeed preaches for moving the combination as upfront therapy, although it is yet to be learned the impact of the

introduction of PARPi as an upfront therapeutic agent in treating prostate cancer patients. Although promising (based on studies with ovarian cancers), long-term PARPi therapy-associated potential toxicity, especially in germline HRD-mutated prostate cancer patients, is yet to be formally studied.[96–99] The observation strongly supports considering the PARPi+ARSI combination as a potential upfront therapy option. Nevertheless, there remains a gap in our understanding of the long-term risks associated with continuous PARPi treatment, especially concerning potential toxicities in prostate cancer patients with inherited HRD mutations. This gap points to a need for thorough clinical investigation to fully grasp the long-term effects of early PARPi intervention in the treatment of prostate cancer in the near future.

Talazoparib as a Treatment Option for Patients with mCRPC

Talazoparib is a PARP inhibitor with a strong PARP trapping ability. Its efficacy as a monotherapy in BRCA-mutated breast cancer is noteworthy, and this extends to its use in combination with enzalutamide for treating metastatic castration-resistant prostate cancer, where it has significantly improved radiographic progression-free survival. The safety and toxicity profile of talazoparib is an essential factor in its therapeutic application. The TALAPRO-2 trial indicated that its use, particularly in combination with enzalutamide, aligns with the known safety profiles of each drug. However, serious adverse reactions such as anemia, fracture, and even Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML) have been observed, albeit at a relatively low incidence.

When comparing talazoparib to other PARP inhibitors like Olaparib, Rucaparib, or Niraparib, its increased myelosuppression stands out, potentially due to its higher potency for PARP trapping.[31,88,100] This highlights the importance of individualized treatment plans, as the choice of a PARP inhibitor often hinges on the cancer type, genetic makeup, and the patient's tolerance to the medication. In clinical settings, it is essential to consider the benefits of talazoparib against its potential risks, tailoring treatment to each patient's unique genetic profile and health background. In research settings, there is a growing interest in conducting systematic studies that compare the efficacy and toxicity of PARPi, specifically between PARP trappers, like talazoparib, and new generations of PARP degraders.[101] The goal is to optimize treatment outcomes while managing adverse effects, ensuring that the use of talazoparib is as safe and effective as possible for the intended patient population.

As the therapeutic landscape of mCRPC continues to evolve, several challenges and opportunities emerge. Firstly, the need a structured and comprehensive genomic profiling to identify patients with DDR mutations who are likely to benefit from PARPi underscores the importance of integrating alternative biomarkers (beyond standard genomic mutation-based HRD determination) that accurately predicts PARPi therapy response into routine clinical practice. Secondly, understanding the mechanisms underlying resistance to PARPi and real-time follow-up of resistance signatures remains crucial for developing next-generation combination therapies and more robust clinical practice. Moreover, the exploration of PARPi beyond *BRCA1/2* and core HRD pathway gene mutations towards a broader spectrum of DDR aberrations (including epigenetic factors involved in HRD, eg aberrations in genes like *ATRX, CHD1*), could expand the therapeutic applicability of these agents.[20,102–104] In the context of combined PARPi and ARSI therapy, the molecular mechanisms underlying acquired resistance in prostate cancer remain to be fully delineated. Comprehensive longitudinal studies are imperative to elucidate these resistance pathways, which is crucial for the informed design and development of future therapeutic strategies. Finally, ongoing and future clinical trials combining PARPi with other therapeutic modalities, including immune checkpoint inhibitors, radiotherapy, and novel targeted agents, promise to further refine and personalize treatment strategies for mCRPC. The advent of PARPi represents a paradigm shift in the management of mCRPC, particularly for tumors harboring DDR gene mutations. By leveraging our growing understanding of prostate cancer's genetic landscape, these targeted therapies offer a beacon of hope for patients with advanced disease. The integration of molecular diagnostics, continued research into resistance mechanisms, and the exploration of combination therapies will be pivotal in realizing the full potential of PARPi in the oncology therapeutic arsenal, marking a significant step towards precision medicine in prostate cancer care.

Disclosure

Dr. Navonil De Sarkar reports grants from Amrican Cancer Society pilot grant through MCW cancer center, outside the submitted work. Dr Subhajit Giri reports grants from Advancing a Healthier Wisconsin Endowment (AHW), outside the

submitted work. Dr Deepak Kilari reports consulting for Pfizer, outside the submitted work. The authors report no other conflicts of interest in this work.

References

1. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. *Ca Cancer J Clin*. 2024;74(1):12–49. doi:10.3322/caac.21820
2. Sandhu S, Moore CM, Chiong E, Beltran H, Bristow RG, Williams SG. Prostate cancer. *Lancet*. 2021;398(10305):1075–1090. doi:10.1016/S0140-6736(21)00950-8
3. Dai C, Dehm SM, Sharifi N. Targeting the androgen signaling axis in prostate cancer. *J Clin Oncol*. 2023;41(26):4267–4278. doi:10.1200/JCO.23.00433
4. Survival rates for prostate cancer. Available from: https://www.cancer.org/cancer/types/prostate-cancer/detection-diagnosis-staging/survival-rates.html. Accessed January 3, 2024
5. Khoshkar Y, Westerberg M, Adolfsson J, et al. Mortality in men with castration-resistant prostate cancer—A long-term follow-up of a population-based real-world cohort. *BJUI Compass*. 2022;3(2):173–183. doi:10.1002/bco2.116
6. Petrylak DP, Tangen CM, Hussain MHA, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med*. 2004;351(15):1513–1520. doi:10.1056/NEJMoa041318
7. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med*. 2004;351(15):1502–1512. doi:10.1056/NEJMoa040720
8. Fizazi K, Scher HI, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol*. 2012;13(10):983–992. doi:10.1016/S1470-2045(12)70379-0
9. Ryan CJ, Smith MR, Fizazi K, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol*. 2015;16(2):152–160. doi:10.1016/S1470-2045(14)71205-7
10. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med*. 2014;371(5):424–433. doi:10.1056/NEJMoa1405095
11. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med*. 2012;367(13):1187–1197. doi:10.1056/NEJMoa1207506
12. Beer TM, Armstrong AJ, Rathkopf D, et al. Enzalutamide in men with chemotherapy-naïve metastatic castration-resistant prostate cancer: extended analysis of the phase 3 prevail study. *Eur Urol*. 2017;71(2):151–154. doi:10.1016/j.eururo.2016.07.032
13. Robinson D, Van Allen EM, Wu YM, et al. Integrative clinical genomics of advanced prostate cancer. *Cell*. 2015;161(5):1215–1228. doi:10.1016/j.cell.2015.05.001
14. Abida W, Cyrta J, Heller G, et al. Genomic correlates of clinical outcome in advanced prostate cancer. *Proc Natl Acad Sci*. 2019;116(23):11428–11436. doi:10.1073/pnas.1902651116
15. Nyquist MD, Corella A, Coleman I, et al. Combined TP53 and RB1 Loss Promotes Prostate Cancer Resistance to a Spectrum of Therapeutics and Confers Vulnerability to Replication Stress. *Cell Rep*. 2020;31(8):107669. doi:10.1016/j.celrep.2020.107669
16. Barbieri CE, Baca SC, Lawrence MS, et al. Exome sequencing identifies recurrent SPOP, FOXA1 and MED12 mutations in prostate cancer. *Nat Genet*. 2012;44(6):685–689. doi:10.1038/ng.2279
17. Wu YM, Cieślik M, Lonigro RJ, et al. Inactivation of CDK12 Delineates a Distinct Immunogenic Class of Advanced Prostate Cancer. *Cell*. 2018;173(7):1770–1782.e14. doi:10.1016/j.cell.2018.04.034
18. Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer. *N Engl J Med*. 2016;375(5):443–453. doi:10.1056/NEJMoa1603144
19. Abeshouse A, Ahn J, Akbani R, et al. The Molecular Taxonomy of Primary Prostate Cancer. *Cell*. 2015;163(4):1011–1025. doi:10.1016/j.cell.2015.10.025
20. Sarkar ND, Dasgupta S, Chatterjee P, et al. Genomic attributes of homology-directed DNA repair deficiency in metastatic prostate cancer. *JCI Insight*. 2021;6(23). doi:10.1172/jci.insight.152789
21. Armenia J, Wankowicz SAM, Liu D, et al. The long tail of oncogenic drivers in prostate cancer. *Nat Genet*. 2018;50(5):645–651. doi:10.1038/s41588-018-0078-z
22. Quigley DA, Dang HX, Zhao SG, et al. Genomic Hallmarks and Structural Variation in Metastatic Prostate Cancer. *Cell*. 2018;174(3):758–769.e9. doi:10.1016/j.cell.2018.06.039
23. van Dessel LF, van Riet J, Smits M, et al. The genomic landscape of metastatic castration-resistant prostate cancers reveals multiple distinct genotypes with potential clinical impact. *Nat Commun*. 2019;10(1):5251. doi:10.1038/s41467-019-13084-7
24. Park JJ, Chu A, Li J, et al. Repeat Next-Generation Sequencing Testing on Progression in Men With Metastatic Prostate Cancer Can Identify New Actionable Alterations. *JCO Precis Oncol*. 2024;8:e2300567. doi:10.1200/PO.23.00567.
25. Deek MP, Van der Eecken K, Phillips R, et al. The Mutational Landscape of Metastatic Castration-sensitive Prostate Cancer: the Spectrum Theory Revisited. *Eur Urol*. 2021;80(5):632–640. doi:10.1016/j.eururo.2020.12.040
26. Labrecque MP, Coleman IM, Brown LG, et al. Molecular profiling stratifies diverse phenotypes of treatment-refractory metastatic castration-resistant prostate cancer. *J Clin Invest*. 2019;129(10):4492–4505. doi:10.1172/JCI128212
27. Marshall CH, Fu W, Wang H, Baras AS, Lotan TL, Antonarakis ES. Prevalence of DNA repair gene mutations in localized prostate cancer according to clinical and pathologic features: association of Gleason score and tumor stage. *Prostate Cancer Prostatic Dis*. 2019;22(1):59–65. doi:10.1038/s41391-018-0086-1
28. Stopsack KH, Nandakumar S, Wibmer AG, et al. Oncogenic Genomic Alterations, Clinical Phenotypes, and Outcomes in Metastatic Castration-Sensitive Prostate Cancer. *Clin Cancer Res*. 2020;26(13):3230–3238. doi:10.1158/1078-0432.CCR-20-0168
29. Polkinghorn WR, Parker JS, Lee MX, et al. Androgen receptor signaling regulates DNA repair in prostate cancers. *Cancer Discov*. 2013;3(11):1245–1253. doi:10.1158/2159-8290.CD-13-0172

30. Asim M, Tarish F, Zecchini HI, et al. Synthetic lethality between androgen receptor signalling and the PARP pathway in prostate cancer. *Nat Commun*. 2017;8(1):374. doi:10.1038/s41467-017-00393-y
31. Zandarashvili L, Langelier MF, Velagapudi UK, et al. Structural basis for allosteric PARP-1 retention on DNA breaks. *Science*. 2020;368(6486): eaax6367. doi:10.1126/science.aax6367
32. Murai J, Huang SYN, Renaud A, et al. Stereospecific PARP trapping by BMN 673 and comparison with olaparib and rucaparib. *Mol Cancer Ther*. 2014;13(2):433–443. doi:10.1158/1535-7163.MCT-13-0803
33. Hopkins TA, Ainsworth WB, Ellis PA, et al. PARP1 Trapping by PARP Inhibitors Drives Cytotoxicity in Both Cancer Cells and Healthy Bone Marrow. *Mol Cancer Res*. 2019;17(2):409–419. doi:10.1158/1541-7786.MCR-18-0138
34. Murai J, Huang SY, Das BB, et al. Trapping of PARP1 and PARP2 by Clinical PARP Inhibitors. *Cancer Res*. 2012;72(21):5588–5599. doi:10.1158/0008-5472.CAN-12-2753
35. Fong PC, Boss DS, Yap TA, et al. Inhibition of Poly(ADP-Ribose) Polymerase in Tumors from BRCA Mutation Carriers. *N Engl J Med*. 2009;361(2):123–134. doi:10.1056/NEJMoa0900212
36. de Bono J, Ramanathan RK, Mina L, et al. Phase I, Dose-Escalation, Two-Part Trial of the PARP Inhibitor Talazoparib in Patients with Advanced Germline BRCA1/2 Mutations and Selected Sporadic Cancers. *Cancer Discovery*. 2017;7(6):620–629. doi:10.1158/2159-8290.CD-16-1250
37. Sandhu SK, Omlin A, Hylands L, et al. Poly (ADP-ribose) polymerase (PARP) inhibitors for the treatment of advanced germline BRCA2 mutant prostate cancer. *Ann Oncol*. 2013;24(5):1416–1418. doi:10.1093/annonc/mdt074
38. Mateo J, Porta N, Bianchini D, et al. Olaparib in patients with metastatic castration-resistant prostate cancer with DNA repair gene aberrations (TOPARP-B): a multicentre, open-label, randomised, phase 2 trial. *Lancet Oncol*. 2020;21(1):162–174. doi:10.1016/S1470-2045(19)30684-9
39. Mateo J, Carreira S, Sandhu S, et al. DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer. *N Engl J Med*. 2015;373(18):1697–1708. doi:10.1056/NEJMoa1506859
40. de Bono J, Mateo J, Fizazi K, et al. Olaparib for Metastatic Castration-Resistant Prostate Cancer. *N Engl J Med*. 2020;382(22):2091–2102. doi:10.1056/NEJMoa1911440
41. Abida W, Patnaik A, Campbell D, et al. Rucaparib in Men With Metastatic Castration-Resistant Prostate Cancer Harboring a BRCA1 or BRCA2 Gene Alteration. *JCO*. 2020;38(32):3763–3772. doi:10.1200/JCO.20.01035
42. Fizazi K, Piulats JM, Reaume MN, et al. Rucaparib or Physician's Choice in Metastatic Prostate Cancer. *N Engl J Med*. 2023;388(8):719–732. doi:10.1056/NEJMoa2214676
43. Smith MR, Scher HI, Sandhu S, et al. Niraparib in patients with metastatic castration-resistant prostate cancer and DNA repair gene defects (GALAHAD): a multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2022;23(3):362–373. doi:10.1016/S1470-2045(21)00757-9
44. de Bono JS, Mehra N, Scagliotti GV, et al. Talazoparib monotherapy in metastatic castration-resistant prostate cancer with DNA repair alterations (TALAPRO-1): an open-label, phase 2 trial. *Lancet Oncol*. 2021;22(9):1250–1264. doi:10.1016/S1470-2045(21)00376-4
45. Li L, Karanika S, Yang G, et al. Androgen receptor inhibitor-induced "BRCAness" and PARP inhibition are synthetically lethal for castration-resistant prostate cancer. *Sci Signal*. 2017;10(480):eaam7479. doi:10.1126/scisignal.aam7479
46. Agarwal N, Zhang T, Efstathiou E, et al. The biology behind combining poly [ADP ribose] polymerase and androgen receptor inhibition for metastatic castration-resistant prostate cancer. *Eur J Cancer*. 2023;192:113249. doi:10.1016/j.ejca.2023.113249
47. Clarke N, Wiechno P, Alekseev B, et al. Olaparib combined with Abiraterone in patients with metastatic castration-resistant prostate cancer: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol*. 2018;19(7):975–986. doi:10.1016/S1470-2045(18)30365-6
48. Agarwal N, Azad AA, Carles J, et al. Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial. *Lancet*. 2023;402(10398):291–303. doi:10.1016/S0140-6736(23)01055-3
49. Clarke NW, Armstrong AJ, Thiery-Vuillemin A, et al. Abiraterone and Olaparib for Metastatic Castration-Resistant Prostate Cancer. *NEJM Evidence*. 2022;1(9):EVIDoa2200043. doi:10.1056/EVIDoa2200043
50. Chi KN, Rathkopf D, Smith MR, et al. Niraparib and Abiraterone Acetate for Metastatic Castration-Resistant Prostate Cancer. *J Clin Oncol*. 2023;41(18):3339–3351. doi:10.1200/JCO.22.01649
51. Hussain MHA, Kocherginsky M, Agarwal N, et al. BRCAAway: a randomized phase 2 trial of Abiraterone, olaparib, or Abiraterone + olaparib in patients with metastatic castration-resistant prostate cancer (mCRPC) bearing homologous recombination-repair mutations (HRRm). *JCO*. 2024;42(4_suppl):19. doi:10.1200/JCO.2024.42.4_suppl.19
52. Saad F, Clarke NW, Oya M, et al. Olaparib plus Abiraterone versus placebo plus Abiraterone in metastatic castration-resistant prostate cancer (PROpel): final prespecified overall survival results of a randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2023;24(10):1094–1108. doi:10.1016/S1470-2045(23)00382-0
53. Research C for DE and FDA DISCO Burst Edition: FDA approval of Lynparza (olaparib), with Abiraterone and prednisone, for BRCA-mutated metastatic castration-resistant prostate cancer. FDA. 2023. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-disco-burst-edition-fda-approval-lynparza-olaparib-abiraterone-and-prednisone-brca-mutated. Accessed January 27, 2024.
54. Chung JH, Dewal N, Sokol E, et al. Prospective Comprehensive Genomic Profiling of Primary and Metastatic Prostate Tumors. *JCO Precis Oncol*. 2019;3(3):1–23. doi:10.1200/PO.18.00283
55. Abida W, Armenia J, Gopalan A, et al. Prospective Genomic Profiling of Prostate Cancer Across Disease States Reveals Germline and Somatic Alterations That May Affect Clinical Decision Making. *JCO Precis Oncol*. 2017;(1):1–16. doi:10.1200/PO.17.00029
56. Beltran H, Yelensky R, Frampton GM, et al. Targeted Next-generation Sequencing of Advanced Prostate Cancer Identifies Potential Therapeutic Targets and Disease Heterogeneity. *Eur Urol*. 2013;63(5):920–926. doi:10.1016/j.eururo.2012.08.053
57. Carreira S, Porta N, Arce-Gallego S, et al. Biomarkers Associating with PARP Inhibitor Benefit in Prostate Cancer in the TOPARP-B Trial. *Cancer Discov*. 2021;11(11):2812–2827. doi:10.1158/2159-8290.CD-21-0007
58. Mateo J, de Bono JS, Fizazi K, et al. Olaparib for the Treatment of Patients With Metastatic Castration-Resistant Prostate Cancer and Alterations in BRCA1 and/or BRCA2 in the PROfound Trial. *J Clin Oncol*. 2024;42(5):571–583. doi:10.1200/JCO.23.00339
59. Nik-Zainal S, Alexandrov LB, Wedge DC, et al. Mutational processes molding the genomes of 21 breast cancers. *Cell*. 2012;149(5):979–993. doi:10.1016/j.cell.2012.04.024
60. Polak P, Kim J, Braunstein LZ, et al. A mutational signature reveals alterations underlying deficient homologous recombination repair in breast cancer. *Nat Genet*. 2017;49(10):1476–1486. doi:10.1038/ng.3934

61. Gulhan DC, Lee JJK, Melloni GEM, Cortés-Ciriano I, Park PJ. Detecting the mutational signature of homologous recombination deficiency in clinical samples. *Nat Genet*. 2019;51(5):912–919. doi:10.1038/s41588-019-0390-2
62. LB Alexandrov, MR Stratton. Mutational signatures: the patterns of somatic mutations hidden in cancer genomes. *Curr Opin Genet Dev*. 2014;24(100): 52–60. doi:10.1016/j.gde.2013.11.014
63. Alexandrov LB, Nik-Zainal S, Wedge DC, et al. Signatures of mutational processes in human cancer. *Nature*. 2013;500(7463):415–421. doi:10.1038/nature12477
64. Alexandrov LB, Kim J, Haradhvala NJ, et al. Author Correction: the repertoire of mutational signatures in human cancer. *Nature*. 2023;614 (7948):E41. doi:10.1038/s41586-022-05600-5
65. Davies H, Glodzik D, Morganella S, et al. HRDetect is a predictor of BRCA1 and BRCA2 deficiency based on mutational signatures. *Nat Med*. 2017;23(4):517–525. doi:10.1038/nm.4292
66. Funnell T, Zhang AW, Grewal D, et al. Integrated structural variation and point mutation signatures in cancer genomes using correlated topic models. *PLoS Comput Biol*. 2019;15(2):e1006799. doi:10.1371/journal.pcbi.1006799
67. Vanderstichele A, Busschaert P, Olbrecht S, Lambrechts D, Vergote I. Genomic signatures as predictive biomarkers of homologous recombination deficiency in ovarian cancer. *Eur J Cancer*. 2017;86:5–14. doi:10.1016/j.ejca.2017.08.029
68. Rosenthal R, McGranahan N, Herrero J, Taylor BS, Swanton C. DeconstructSigs: delineating mutational processes in single tumors distinguishes DNA repair deficiencies and patterns of carcinoma evolution. *Genome Biol*. 2016;17(1):31. doi:10.1186/s13059-016-0893-4
69. Sztupinszki Z, Diossy M, Krzystanek M, et al. Migrating the SNP array-based homologous recombination deficiency measures to next generation sequencing data of breast cancer. *Npj Breast Cancer*. 2018;4(1):1–4. doi:10.1038/s41523-018-0066-6
70. Taza F, Holler AE, Fu W, et al. Differential Activity of PARP Inhibitors in BRCA1- Versus BRCA2-Altered Metastatic Castration-Resistant Prostate Cancer. *JCO Precis Oncol*. 2021;5:PO.21.00070. doi:10.1200/PO.21.00070
71. Orme JJ, Taza F, De Sarkar N, et al. Co-occurring BRCA2/SPOP Mutations Predict Exceptional Poly (ADP-ribose) Polymerase Inhibitor Sensitivity in Metastatic Castration-Resistant Prostate Cancer. *Eur Urol Oncol*. 2023;7(4):S2588–9311(23)00277–8. doi:10.1016/j.euo.2023.11.014
72. Messina C, Giunta EF, Signori A, et al. Combining PARP Inhibitors and Androgen Receptor Signalling Inhibitors in Metastatic Prostate Cancer: a Quantitative Synthesis and Meta-analysis. *Eur Urol Oncol*. 2023:S2588–9311(23)00155–4. doi:10.1016/j.euo.2023.07.013.
73. Fallah J, Xu J, Weinstock C, et al. Efficacy of Poly(ADP-ribose) Polymerase Inhibitors by Individual Genes in Homologous Recombination Repair Gene-Mutated Metastatic Castration-Resistant Prostate Cancer: a US Food and Drug Administration Pooled Analysis. *JCO*. 2024. doi:10.1200/JCO.23.02105.
74. Ledermann JA, Oza AM, Lorusso D, et al. Rucaparib for patients with platinum-sensitive, recurrent ovarian carcinoma (ARIEL3): post-progression outcomes and updated safety results from a randomised, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2020;21 (5):710–722. doi:10.1016/S1470-2045(20)30061-9
75. Antonarakis ES, Gomella LG, Petrylak DP. When and How to Use PARP Inhibitors in Prostate Cancer: a Systematic Review of the Literature with an Update on On-Going Trials. *Eur Urol Oncol*. 2020;3(5):594–611. doi:10.1016/j.euo.2020.07.005
76. Castro E, Romero-Laorden N, Del Pozo A, et al. PROREPAIR-B: a prospective cohort study of the impact of germline DNA repair mutations on the outcomes of patients with metastatic castration-resistant prostate cancer. *J Clin Oncol*. 2019;37(6):490–503. doi:10.1200/JCO.18.00358
77. Ao S, Ey Y, Hh C. Honing in on PARPi response in prostate cancer: from hr pathway to gene-by-gene granularity. *Clin Cancer Res*. 2020;26 (11). doi:10.1158/1078-0432.CCR-20-0707
78. Tobalina L, Armenia J, Irving E, O'Connor MJ, Forment JV. A meta-analysis of reversion mutations in BRCA genes identifies signatures of DNA end-joining repair mechanisms driving therapy resistance. *Ann Oncol*. 2021;32(1):103–112. doi:10.1016/j.annonc.2020.10.470
79. Congregado B, Rivero I, Osmán I, Sáez C, Medina López R. PARP inhibitors: a new horizon for patients with prostate cancer. *Biomedicines*. 2022;10(6):1416. doi:10.3390/biomedicines10061416
80. Kwon WA. PARP inhibitors in the treatment of prostate cancer: from scientific rationale to clinical development. *World J Mens Health*. 2024;42 (2):290–303. doi:10.5534/wjmh.230177
81. Chi KN, Rathkopf DE, Smith MR, et al. Phase 3 MAGNITUDE study: first results of niraparib (NIRA) with abiraterone acetate and prednisone (AAP) as first-line therapy in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) with and without homologous recombination repair (HRR) gene alterations. *JCO*. 2022;40(6_suppl):12. doi:10.1200/JCO.2022.40.6_suppl.012
82. Piulats JM, Azad AA, Laird AD, et al. Abstract CT018: TMPRSS2-ERG and RB1 as candidate predictive biomarkers for efficacy in TALAPRO-2: phase 3 study of talazoparib (TALA) + enzalutamide (ENZA) vs placebo (PBO) + ENZA as first-line (1L) treatment in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). *Cancer Res*. 2024;84(7_Supplement):CT018. doi:10.1158/1538-7445.AM2024-CT018
83. Moore K, Colombo N, Scambia G, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med*. 2018;379(26):2495–2505. doi:10.1056/NEJMoa1810858
84. Me R, Sa I, S E, et al. OlympiAD extended follow-up for overall survival and safety: olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. *Eur. J. Cancer*. 2023;184. doi:10.1016/j.ejca.2023.01.031
85. Robson ME, Tung N, Conte P, et al. OlympiAD final overall survival and tolerability results: olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. *Ann Oncol*. 2019;30(4):558–566. doi:10.1093/annonc/mdz012
86. Weigelt B, Comino-Méndez I, de Bruijn I, et al. Diverse BRCA1 and BRCA2 reversion mutations in circulating cell-free DNA of therapy-resistant breast or ovarian cancer. *Clin Cancer Res*. 2017;23(21):6708–6720. doi:10.1158/1078-0432.CCR-17-0544
87. Walmsley CS, Jonsson P, Cheng ML, et al. Convergent evolution of BRCA2 reversion mutations under therapeutic pressure by PARP inhibition and platinum chemotherapy. *NPJ Precis Oncol*. 2024;8(1):34. doi:10.1038/s41698-024-00526-9
88. LaFargue CJ, Dal Molin GZ, Sood AK, Coleman RL. Exploring and comparing adverse events between PARP inhibitors. *Lancet Oncol*. 2019;20(1):e15–e28. doi:10.1016/S1470-2045(18)30786-1
89. Ren X, Ji Z, McHale CM, et al. The impact of FANCD2 deficiency on formaldehyde-induced toxicity in human lymphoblastoid cell lines. *Arch Toxicol*. 2013;87(1):189–196. doi:10.1007/s00204-012-0911-6

90. Loibl S, O'Shaughnessy J, Untch M, et al. Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrighTNess): a randomised, phase 3 trial. *Lancet Oncol*. 2018;19(4):497–509. doi:10.1016/S1470-2045(18)30111-6
91. Kaye SB, Lubinski J, Matulonis U, et al. Phase II, open-label, randomized, multicenter study comparing the efficacy and safety of olaparib, a poly (ADP-ribose) polymerase inhibitor, and pegylated liposomal doxorubicin in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer. *J Clin Oncol*. 2012;30(4):372–379. doi:10.1200/JCO.2011.36.9215
92. Dellavedova G, Decio A, Formenti L, et al. The PARP1 inhibitor azd5305 impairs ovarian adenocarcinoma progression and visceral metastases in patient-derived xenografts alone and in combination with carboplatin. *Cancer Res Commun*. 2023;3(3):489–500. doi:10.1158/2767-9764.CRC-22-0423
93. Mirza Mansoor R, Monk Bradley J, Herrstedt J, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. *N Engl J Med*. 2016;375(22):2154–2164. doi:10.1056/NEJMoa1611310
94. Talia G, Pascal H, Michele R, et al. Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. *N Engl J Med*. 2019;381(4):317–327. doi:10.1056/NEJMoa1903387
95. Welch EC, Torres A, Miller J, et al. A phase II single-arm trial of niraparib in platinum-sensitive metastatic castration-resistant prostate cancer with DNA repair defects (PLATPARP). *JCO*. 2024;42(4_suppl):TPS255. doi:10.1200/JCO.2024.42.4_suppl.TPS255
96. Chelariu-Raicu A, Trillsch F, Burges A, et al. PARP inhibitors: risk factors for toxicity and matching patients to the proper poly (ADP-ribose) polymerase inhibitor (PARPi) therapy. *Int J Gynecologic Cancer*. 2023;33(5):812–822. doi:10.1136/ijgc-2022-003990
97. Shu Y, Ding Y, He X, Liu Y, Wu P, Zhang Q. Hematological toxicities in PARP inhibitors: a real-world study using FDA adverse event reporting system (FAERS) database. *Cancer Med*. 2023;12(3):3365–3375. doi:10.1002/cam4.5062
98. Mirza MR, Benigno B, Dørum A, et al. Long-term safety in patients with recurrent ovarian cancer treated with niraparib versus placebo: results from the phase III ENGOT-OV16/NOVA trial. *Gynecologic Oncol*. 2020;159(2):442–448. doi:10.1016/j.ygyno.2020.09.006
99. Saad F, Armstrong AJ, Oya M, et al. Tolerability of olaparib combined with abiraterone in patients with metastatic castration-resistant prostate cancer: further results from the phase 3 propel trial. *Eur Urol Oncol*. 2024. doi:10.1016/j.euo.2024.03.006
100. Bao S, Yue Y, Hua Y, et al. Safety profile of poly (ADP-ribose) polymerase (PARP) inhibitors in cancer: a network meta-analysis of randomized controlled trials. *Ann Transl Med*. 2021;9(15):1229. doi:10.21037/atm-21-1883
101. Kim C, Chen C, Yu Y. Avoid the trap: targeting PARP1 beyond human malignancy. *Cell Chem Biol*. 2021;28(4):456–462. doi:10.1016/j.chembiol.2021.02.004
102. Juhász S, Elbakry A, Mathes A, Löbrich M. ATRX promotes DNA repair synthesis and sister chromatid exchange during homologous recombination. *Mol Cell*. 2018;71(1):11–24.e7. doi:10.1016/j.molcel.2018.05.014
103. Elbakry A, Juhász S, Chan KC, Löbrich M. ATRX and RECQ5 define distinct homologous recombination subpathways. *Proc Natl Acad Sci*. 2021;118(3):e2010370118. doi:10.1073/pnas.2010370118
104. Kari V, Mansour WY, Raul SK, et al. Loss of CHD1 causes DNA repair defects and enhances prostate cancer therapeutic responsiveness. *EMBO Rep*. 2016;17(11):1609–1623. doi:10.15252/embr.201642352