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REVIEW ARTICLE

Combination of PARP Inhibitors and Androgen Receptor Pathway Inhibitors in Metastatic Castration-Resistant Prostate Cancer

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Abstract

Despite recent advances in the treatment of metastatic prostate cancer, progression to a castration-resistant state remains inevitable for most and prognosis is limited. Genetic testing for homologous recombination repair pathway alterations is recommended for all patients with advanced prostate cancer given that a mutation is present in up to 25% of cases. Poly(ADP-ribose) polymerase (PARPis) are now approved for use in patients with metastatic castration-resistant prostate cancer who have progressed on an androgen receptor pathway inhibitor (ARPI) and harbour a germline or somatic homologous recombination repair mutation. Preclinical data support a synergistic effect with an ARPI and PARPi, and various ARPI-PARPi combinations have therefore been explored in phase III clinical trials. Despite heterogeneous findings, a clear hierarchy of benefit is evident, with patients harbouring a *BRCA* mutation deriving the greatest magnitude of benefit, followed by any homologous recombination repair mutation. The benefit in homologous recombination repair-proficient cohort is less clear, and questions remain about whether ARPI-PARPi combination therapy should be offered to patients without a homologous recombination repair mutation. With ARPIs now considered standard-of-care for metastatic hormone-sensitive prostate cancer, ARPI-PARPi combination therapy is currently being explored earlier in the treatment paradigm. The purpose of this review is to discuss the rationale behind ARPI-PARPi combination therapy, summarise the results of key clinical trials, and discuss clinical considerations and future perspectives.

1 Introduction

Prostate cancer is the second most common cancer in men, with over 1.4 million new cases diagnosed globally in 2020 [1] and an incidence predicted to significantly increase to 2.9 million by 2040 [2]. The prevalence of metastatic prostate cancer, in particular, is rising [3], and remains incurable with high morbidity.

Since the discovery of testosterone dependency in prostate cancer in 1941 [4], androgen deprivation therapy (ADT) has formed the backbone of treatment for metastatic disease. The treatment landscape has significantly evolved over the last two decades, with multiple novel therapies now integrated into the therapeutic paradigm. Standard systemic treatments for metastatic hormone-sensitive prostate cancer (mHSPC) include taxane-based chemotherapy (docetaxel) and androgen receptor pathway inhibitors (ARPI) in combination with ADT. Despite these early interventions, however, progression to metastatic castration-resistant prostate cancer (mCRPC) remains inevitable for most. Several additional therapies are available to treat mCRPC, such as further taxane chemotherapy with cabazitaxel, an alternate ARPI, poly(ADP-ribose) polymerase inhibitors (PARPi) and targeted radioligand therapy such as [^{177}Lu]Lu-PSMA and radium-223 [5]. Prognosis remains poor[6], however, and further research into mechanisms of treatment resistance and strategies to overcome these are crucial.

The transition to mCRPC is largely driven by alterations in the androgen receptor (AR). These alterations include AR ligand-binding domain mutations, AR overexpression, and AR splice-variants (AR-V), which can restore AR signalling despite ongoing androgen suppression from ADT [7]. As such, the AR signalling pathway forms a key therapeutic target and various ARPIs, such as enzalutamide and abiraterone acetate, have been evaluated and approved for

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Key Points

Androgen receptor pathway inhibitors (ARPI) and poly(ADP-ribose) polymerase inhibitors (PARPi) are already established treatment options for patients with metastatic prostate cancer. Given pre-clinical data suggesting synergy between the two agents, several studies have evaluated ARPI-PARPi combinations in metastatic castration-resistant prostate cancer.

The greatest survival benefit with an ARPI-PARPi combination compared to an ARPI alone is seen in patients with metastatic castration-resistant prostate cancer who have a *BRCA* mutation. Improvements in survival are seen in the overall subgroup of patients with any homologous recombination repair mutation, though differential results are seen depending on the gene involved.

Questions remain about the benefit of an ARPI-PARPi combination in patients without a homologous recombination repair mutation, and the optimal sequencing in the evolving prostate cancer treatment landscape.

use in mCRPC [8–10]. Some AR alterations, however, lead to constitutive activation of the AR pathway resulting in a state of androgen independence, with inherent resistance to ARPIs [11]. Other resistance mechanisms leading to castration resistance include aberrations in DNA repair genes (in particular, the homologous recombination repair [HRR] pathway) and loss of tumour suppressor genes [12, 13]. In patients with mCRPC, the prevalence of somatic and germline pathogenic HRR mutations is increased compared with in localised or hormone-sensitive disease, reaching 20–25% and 12%, respectively [14]. The *BRCA1* and *BRCA2* genes play critical roles in the HRR pathway, with germline and somatic *BRCA* aberrations being present in 5% and 11% of mCRPC, respectively [15]. Alterations in the HRR-related genes, especially *BRCA*, confer a poor prognosis [16–20]. Currently, the recommendation for genomic testing to assess *BRCA* and HRR mutation status is incorporated into most guidelines and consensus statements, though optimal timing and methods of HRR gene testing vary [21].

In patients with HRR-mutant (HRRm) prostate cancer, double-stranded DNA breaks are unable to be repaired via the HRR pathway. Consequently, alternative non-conservative pathways of DNA repair are preferentially utilised, such as non-homologous end joining or traditional single-strand DNA repair pathways (e.g. the poly(ADP-ribose) polymerase [PARP]-mediated nucleotide excision repair [NER] or base-excision repair [BER] pathways) [22–24]. Given such pathways do not use a homologous DNA sequence to guide repair, they may lead to the accumulation of other DNA alterations such as deletions, conferring an increased risk of cancer developing. If the non-conservative pathway is also inhibited or non-functional, DNA repair cannot occur and cell death ensues.

Poly(ADP-ribose) polymerase inhibitors have therefore emerged as a potential therapeutic option for HRRm patients, exploiting synthetic lethality through disruption of the NER/BER pathways (see Fig. 1). The lack of a functional NER/BER pathway results in increased degradation of single-strand DNA breaks into double-strand breaks, which are then unable to be repaired with high fidelity in HRRm cells. PARP1 and PARP2 are the two predominant enzymes involved with sensing DNA damage and facilitating repair. The catalytic function of each enzyme becomes activated at DNA damage sites, which leads to DNA repair through the NER/BER pathway. Once repaired, PARP releases itself from the DNA through a process called autoPARylation. Most PARPis target primarily PARP1 and PARP2, and to varying degrees also prevent release of PARP molecules from sites of DNA damage—a process known as PARP trapping [25]. The net result of these effects is prevention of DNA repair, leading to cell death.

2 PARP Inhibitors as Monotherapy in Metastatic Castration-Resistant Prostate Cancer

Use of PARPis as monotherapy is now considered standard of care for patients with mCRPC harbouring either a somatic or germline pathogenic *BRCA* mutation. Several single-arm phase II trials evaluated various PARPis in HRRm patients with mCRPC and demonstrated a consistent benefit in the objective response rate (ORR). The TOPARP-B (olaparib) [26], TRITON-2 (rucaparib) [27], and TALAPRO-1 (talazoparib) [28] trials included patients with mono- and biallelic HRR alterations who had progressed after a prior taxane and ARPI (prior ARPI optional in TOPARP-B). The ORR in the *BRCA1/2* cohorts in each study were 83.3%, 43.5% and 46%, respectively, with lower response rates seen for other HRR gene subgroups. Of note, the TOPARP-B trial adopted a non-standard definition of ORR, which included a composite of at least a 50% reduction in prostate-specific antigen level, conversion of circulating tumour cells from ≥ 5 per 7.5 mL of blood to <5/7.5 mL, in addition to RECIST defined objective response. The GALAHAD trial (niraparib) only included patients with bi-allelic or germline HRR alterations, and the ORR for *BRCA1/2* patients was 34.2% [29]. Consequently, two randomised trials were then performed comparing the use of a PARPi to standard-of-care treatment in mCRPC.

The PROfound trial was a phase III trial comparing olaparib 300 mg twice daily (BD) to physician's choice of ARPI

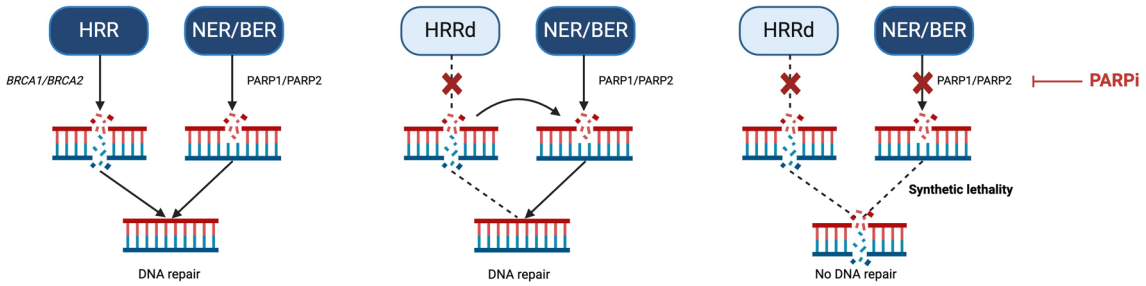

Fig. 1 Mechanism of action of poly(ADP-ribose) polymerase inhibitors (PARPi) in a homologous recombination repair pathway-deficient (HRRd) cell resulting in synthetic lethality. *BER* base excision repair pathway, *BRCA1* BReast CAncer gene 1, *BRCA2* BReast CAncer gene 2, *NER* nucleotide excision repair pathway. Created with BioRender.com

switch (enzalutamide or abiraterone acetate) in patients with mCRPC who had progressed on a prior ARPI. Patients were tested for 15 different HRR genes and were eligible if they had a pathogenic alteration detected. Patients harbouring a *BRCA1*, *BRCA2* or *ATM* mutation formed Cohort A, with the remaining HRR mutations allocated to Cohort B. Approximately 65% of patients overall had received at least one prior taxane. The primary endpoint of radiographic progression-free survival (rPFS) in Cohort A was met (median rPFS 7.4 vs 3.6 months, hazard ratio [HR] 0.34 [95% confidence interval (CI) 0.25–0.47], $p < 0.001$), with a lower magnitude of benefit seen with Cohorts A and B combined (5.8 vs 3.5 months, HR 0.49 [95% CI 0.38–0.63], $p < 0.001$) [30]. The final overall survival (OS) favoured the experimental arm for Cohort A (19.1 vs 14.7 months, HR 0.69 [95% CI 0.50–0.97], $p = 0.02$), and in both cohorts to a lesser degree (17.3 vs 14.0 months, HR 0.79 [95% CI 0.61–1.03]) [31]. A post-hoc gene-by-gene analysis found that the *ATM* subgroup in Cohort A did not derive significant benefit from treatment with olaparib (median rPFS 5.4 months, HR 1.04 [95% CI 0.61–1.87], median OS 18.0 months, HR 0.93 [95% CI 0.53–1.75]) [32]. Further analysis of the *BRCA* subgroup found that the extent of OS benefit was greater in patients who were naïve to chemotherapy (median OS for previous taxane subgroup 17.4 vs 12.6 months, HR 0.64 [95% CI 0.39–1.08]; compared with no previous taxane subgroup, not reached [NR] versus 18.8 months, HR 0.30 [95% CI 0.10–0.78]) [33].

The TRITON-3 phase III trial compared rucaparib 600 mg BD to physician's choice of either docetaxel or ARPI switch in patients with mCRPC harbouring a *BRCA1, BRCA2* or *ATM* mutation [34]. The primary outcome of rPFS was met and favoured rucaparib, with the greatest benefit seen in the *BRCA* subgroup (median rPFS 11.2 vs 6.4 months, HR 0.50 [95% CI 0.36–0.69], $p < 0.001$) followed by the intention-to-treat group (10.2 vs 6.4 months, HR 0.61 [95% CI 0.47–0.80], $p < 0.001$). Importantly, the TRITON-3 trial is the only trial evaluating a PARPi in mCRPC that incorporated an upfront chemotherapy comparator. In this study, *BRCA*-mutant patients had longer rPFS if they received rucaparib after progression on a prior ARPI, compared with docetaxel (11.2 vs 8.3 months, HR 0.53 [95% CI 0.37–0.77]), which is consistent with the post-hoc analysis findings in the PROfound trial and suggests that a PARPi should be prioritised before chemotherapy for these patients. An exploratory analysis of the *ATM* subgroup did not show a significant rPFS benefit (8.1 vs 6.8 months, HR 0.95 [95% CI 0.59–1.52]).

As a result of these studies, in 2020 the US Food and Drug Administration (FDA) first approved olaparib for use as monotherapy in patients with mCRPC with a pathogenic germline or somatic HRR mutation, after progression on an ARPI [35]. This was followed by approval of rucaparib in patients with mCRPC harbouring a pathogenic germline or somatic *BRCA* mutation, who have received a prior ARPI and taxane [36]. The European Medicines Agency subsequently approved the use of olaparib as monotherapy for patients with mCRPC; however, the approval was restricted to include *BRCA* mutations only [37].

3 Rationale for Combining PARP Inhibitors with ARPIs

Preclinical in vitro models have demonstrated the potential for synergy between ARPIs and PARPis through a number of mechanisms (see Fig. 2), raising the question of whether their use in combination can be extended to a wider population of patients regardless of HRR mutation status. First, ARPIs inhibit downstream transcriptional activity of the AR, which includes several genes involved in the HRR pathway [38]. This induces a functional HRR-deficient state, or a 'BRCAness' phenotype, which then potentiates PARPi activity [38, 39]. Second, PARP enzymes are involved with recruiting the AR to its transcription site, thereby augmenting the AR signalling pathway and promoting an

androgen-independent state [40, 41]. It follows then that PARP enzyme inhibition via a PARPi should reduce AR signalling activity. Poly(ADP-ribose) polymerase enzyme activity is also increased in advanced prostate cancer, particularly in mCRPC, which thereby may increase sensitivity to PARPis [38, 40, 42].

The addition of a PARPi may also attenuate mechanisms of resistance to ARPIs. One key mechanism that drives castration resistance is mutations in the AR, in particular, through the development of ligand-binding domain mutations and AR-Vs, which lack a functional ligand-binding domain [43]. AR splice-variants in particular are dependent on the catalytic function of PARP enzymes for transcriptional activation, with evidence demonstrating that PARP inhibition compromises the expression of AR-V-dependent genes and promotes sensitivity to ARPIs [44]. Another potential mechanism of resistance to an ARPI is through loss of the *RB1* gene, which is commonly co-deleted with *BRCA2* due to their proximity on chromosome 13q. *RB1* and *BRCA2* co-deletion has been reported in up to 50% of patients with metastatic prostate cancer and is associated with a more aggressive disease phenotype [45] with a less durable response to ARPIs [46]. The addition of a PARPi in cases of *RB1-BRCA2* co-deletion may, therefore, potentially overcome the resultant ARPI resistance and improve efficacy.

4 Phase III Trials Evaluating an ARPI-PARPi Combination in Metastatic Castration-Resistant Prostate Cancer

Several early-phase trials have investigated the efficacy of PARPis and ARPIs in combination in patients with mCRPC. Notably, a randomised phase II trial first evaluating the combination of olaparib with abiraterone acetate enrolled 142 patients with mCRPC previously treated with docetaxel [47]. Patients were randomised regardless of HRR mutation status to receive either olaparib 300 mg BD or placebo in combination with abiraterone acetate 1000 mg daily and prednisolone 10 mg daily. The primary endpoint was investigator-assessed rPFS, which favoured the experimental arm in the intention-to-treat cohort (13.8 months vs 8.2 months, HR 0.65 [95% CI 0.44–0.97], $p = 0.034$). Analysis of the germline and circulating tumour DNA (ctDNA) plasma samples collected during this study found that the rPFS benefit of the ARPI-PARPi combination possibly extended to the non-HRRm cohort (HR 0.54 [95% CI 0.32–0.93]), suggesting that the synergistic effect of the PARPi-ARPI combination may exist irrespective of HRR mutational status [48]. Building on this pre-clinical and early clinical data, three pivotal phase III trials were performed evaluating different variations of PARPi-ARPI combinations

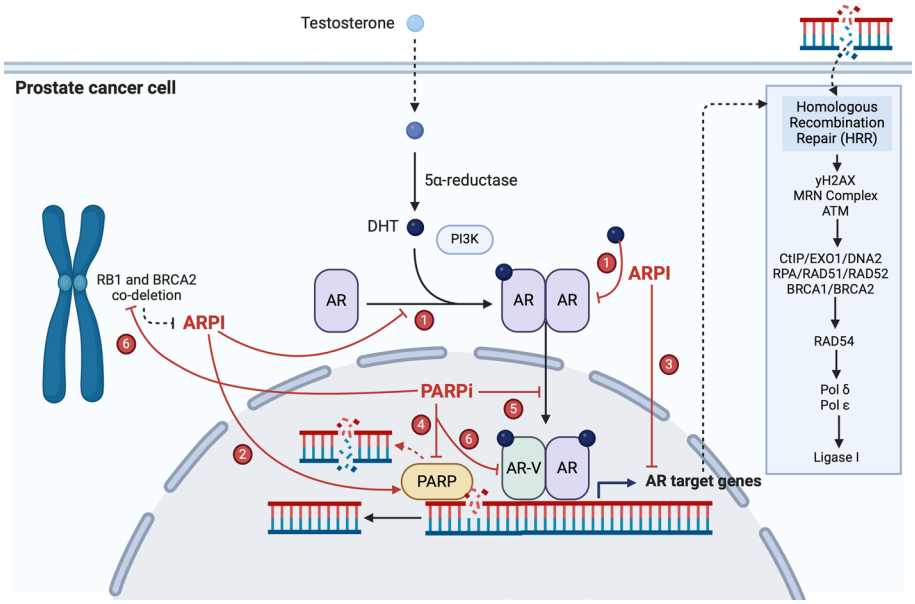

Fig. 2 Mechanisms of action of poly(ADP-ribose) polymerase inhibitor (PARPis) and androgen receptor pathway inhibitors (ARPI) in advanced prostate cancer. *AR-V* AR splice variant, *ARPI* androgen receptor pathway inhibitor, AR androgen receptor, *DHT* dihydrotestosterone. ARPI suppresses AR activity (1), upregulates poly(ADP-ribose) polymerase (PARP) activity (2), and downregulates the homologous recombination repair (HRR) gene expression (3) thereby inducing a phenotype resembling HRR deficiency (BRCAness). PARPi disrupt single-strand DNA repair (4), leading to cytotoxic double-stranded DNA breaks, suppressing AR transcriptional activity (5), and may attenuate mechanisms of resistance to ARPIs mediated by co-deletion of *RB1* and *BRCA2* or AR-Vs (6). Created with BioRender.com

in the first-line mCRPC setting — PROpel, MAGNITUDE and TALAPRO-2.

In the phase III PROpel trial, 796 patients with mCRPC were randomised 1:1 to receive olaparib 300 mg BD or placebo, in combination with abiraterone acetate 1000 mg and prednisolone 10 mg daily [49, 50]. Patients were naïve to treatment in the mCRPC setting and were permitted to have received prior docetaxel if given in the localised or mHSPC settings, and an ARPI (other than abiraterone acetate) if ceased at least 12 months prior to randomisation. The primary endpoint was investigator-assessed rPFS, with OS as a key secondary endpoint. Patients were stratified according to location of metastatic sites, and prior exposure to docetaxel. HRR mutation status was not known at the time of enrolment and randomisation, and genomic testing was performed retrospectively using plasma ctDNA (using FoundationOne Liquid CDX) and/or tissue (using FoundationOne CDX) samples. Based on these results, patients were classified as either HRRm (see Table 1 for list of genes tested), non-HRRm or HRRm unknown. The primary analysis revealed that the median rPFS in the intention-to-treat cohort was significantly longer in the experimental arm compared with the control arm (24.8 vs 16.6 months, HR 0.66 [95% CI 0.54–0.81], $p < 0.001$). All pre-specified HRRm gene subgroups benefitted more from the experimental arm, with the greatest magnitude of benefit seen in patients with a *BRCA* mutation (HR 0.23 [95% CI 0.12–0.43]), followed by the overall HRRm subgroup (HR 0.50 [95% CI 0.34–0.73]) and then non-HRRm (HR 0.76 [95% CI 0.60–0.97]). The final OS analysis (median follow-up time of 36.6 months) also favoured the experimental arm in the intention-to-treat population (42.1 vs 34.7 months, HR 0.81 [95% CI 0.67–1.00], $p = 0.054$). The greatest OS benefit was again seen in the *BRCA* subgroup (HR 0.29 [95% CI 0.14–0.56]), with the benefit less clear in the non-HRRm subgroup (HR 0.89 [95% CI 0.70–1.14]) [49]. Though adverse events were in keeping with the known toxicity profile of either drug, the addition of olaparib to abiraterone acetate did increase toxicity overall. Most notably, anaemia was the most common adverse event occurring in 50% of patients compared with 18% in the control group (grade 3 or higher anaemia occurring in 16% vs 3%, respectively). Seventy-two (18%) patients required at least one blood transfusion in the experimental arm. A higher rate of venous thromboembolism (9% vs 4%), fatigue (39% vs 30%), nausea (31% vs 14%) and diarrhoea (21% vs 11%) were also noted. Following these results, olaparib in combination with abiraterone acetate and prednisolone was approved by the FDA for use in patients with mCRPC with a *BRCA* mutation only [51]. Conversely, the European Medicines Agency approved the combination in 2022 for use in all patients with mCRPC for whom chemotherapy is not clinically indicated [52].

The benefit of olaparib and abiraterone acetate compared to either agent alone in patients with inactivating germline or somatic *BRCA1*, *BRCA2* or *ATM* mutant mCRPC was further evaluated in the ongoing phase II BRCAAway study (NCT03012321). In this trial, 165 patients were randomised to either abiraterone acetate, olaparib or the combination with cross-over permitted in the monotherapy arms. Importantly, the combination arm had a significantly longer median PFS of 39 months (compared with 14 months in olaparib arm, HR 0.32 [95% CI 0.14–0.75] and 8.4 months in the abiraterone acetate arm, HR 0.28 [95% CI 0.13–0.65]). These results possibly support combining abiraterone acetate and olaparib rather than using these drugs sequentially, though the study is limited by small patient numbers, and OS is yet to be reported [53].

The phase III MAGNITUDE trial similarly evaluated the combination of niraparib 200 mg daily versus placebo in combination with abiraterone acetate and prednisolone as first-line therapy for patients with mCRPC [54]. Patients could have received prior docetaxel in the mHSPC setting, and up to a 4-month lead-in of abiraterone acetate for mCRPC prior to enrolment. Patients underwent prospective testing for HRR status (see Table 1 for genes tested) using tissue and/or plasma samples. In contrast to the PROpel trial, these results then informed which cohort the patients would enrol into (HRRm vs non-HRRm) and were randomised 1:1 subsequently to either treatment arm. The primary endpoint was rPFS according to blinded independent central review. The first interim analysis and pre-planned futility analysis of the non-HRRm cohort found no benefit with adding niraparib to abiraterone acetate for the prespecified composite endpoint (first of prostate-specific antigen progression or rPFS) [HR 1.09; 95% CI 0.75–1.57] [55]. Consequently, futility was declared and the non-HRRm cohort was closed to enrolment following this analysis. The second interim analysis was performed after a median follow-up of 24.8 months for the *BRCA1/2* subgroup and 26.8 months for the HRRm cohort (423 patients). The median rPFS in the *BRCA1/2* subgroup was 19.5 versus 10.9 months (HR 0.55 [95% CI 0.39–0.78], $p = 0.0007$), with the benefit also extending to the HRRm cohort (HR 0.76 [95% CI 0.60–0.97], $p = 0.028$). A pre-specified analysis of patients harbouring a mutation in *ATM*, *BRIP1*, *CDK12*, *CHEK2*, *FANCA*, *HDAC2* and *PALB2* was performed, which demonstrated favourable rPFS outcomes for all patients except for those with *ATM* and *CDK12* mutations. Overall survival at this timepoint was immature; however, favoured the experimental arm for the *BRCA1/2* cohort but *not* the HRRm cohort (HR 0.88 [95% CI 0.58–1.34], $p = 0.5505$; vs HR 1.01 [95% CI 0.75–1.36], $p = 0.948$) [54]. A pre-specified inverse probability censoring weighting analysis of OS, which considered subsequent life-prolonging therapies including PARPi use, reported favourable survival outcomes

Table 1 Pivotal phase III clinical trials evaluating PARPi and ARPI in mCRPC

	PROpel [49, 50]	MAGNITUDE [54, 55]	TALAPRO-2 [59, 60]
Study design			
Clinical trial number	NCT03732820	NCT03748641	NCT03395197
Interventional arm treatment (*N*)	Olaparib 300 mg BD + abiraterone acetate 1000 mg daily + prednisolone 5 mg BD (399)	Niraparib 200 mg daily + abiraterone acetate 1000 mg daily + prednisolone 10 mg daily (212)	Talazoparib 0.5 mg daily + enzalutamide 160 mg daily (402)
Control arm treatment (*N*)	Placebo + abiraterone acetate 1000 mg daily + prednisolone 5 mg BD (397)	Placebo + abiraterone acetate 1000 mg daily + prednisolone 10 mg daily (211)	Placebo + enzalutamide 160 mg daily (403)
Crossover	Not allowed	Patients could request to be unblinded	Not allowed
Key eligibility	First-line mCRPC ECOG 0-1 All-comers regardless of HRR status	First-line mCRPC ECOG 0-1 All-comers stratified into 2 experimental cohorts (HRRm and non-HRRm)	First-line mCRPC ECOG 0–1 All-comers regardless of HRR status
Prior docetaxel	Docetaxel allowed at local and mHSPC stage	Docetaxel allowed at mHSPC or nmCRPC stage	Docetaxel allowed at mHSPC stage
Prior ARPI	Prior ARPI allowed if stopped ≥12 months prior to enrolment (prior abiraterone acetate not allowed)	Prior ARPI allowed for mHSPC or nmCRPC Prior abiraterone acetate for up to 4 months in mCRPC allowed prior to enrolment	Prior abiraterone acetate or orteronel allowed in mHSPC
Stratification factors	Metastatic site Prior docetaxel in mHSPC setting	Prior taxane exposure Prior ARPI exposure Prior abiraterone acetate use HRRm cohort: *BRCA1/2* vs other HRR gene alterations	Prior abiraterone acetate or docetaxel in mHSPC setting HRR alteration status
Molecular profiling			
Profiling approach	Retrospective	Prospective	Prospective
HRR genes tested	*ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L*	*ATM, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, HDAC2, PALB2*	*BRCA1, BRCA2, PALB2, ATM, ATR, CHEK2, FANCA, RAD51C, NBN, MLH1, MRE11A, CDK12*
HRR testing source	Tumour tissue (FoundationOne®CDx) and/or blood samples (FoundationOne®Liquid CDx)	Tumour tissue (FoundationOne®CDx) and/or blood samples (Resolution Biosciences)	Tumour tissue (FoundationOne®CDx) and/or blood samples (FoundationOne®Liquid CDx)
Tissue HRR testing (%)	68%	69% (HRR+ cohort)	100%
HRRm (%)	28%	100%	21%
Prior therapies			
Docetaxel	24%	20%	21%
Prior ARPI for mHSPC/nmCRPC	0.3%	3.7%	6%
Prior ARPI for 1L mCRPC	0%	23%	0%
Any grade ≥3 AE			
Experimental arm	56%	72.2%	75%
Control arm	43%	49.3%	45%

Table 1 (continued)

	PROpel [49, 50]	MAGNITUDE [54, 55]	TALAPRO-2 [59, 60]
Dose reduction			
Experimental arm	23%, olaparib/placebo 3% abiraterone acetate	20.3%	53%, talazoparib/placebo 15%, enzalutamide
Control arm	6% olaparib/placebo 4% abiraterone acetate	3.8%	7%, talazoparib/placebo 8%, enzalutamide
Treatment discontinuation			
Experimental arm	17%, olaparib/placebo 11%, abiraterone acetate	15.1%	19% (8% due to anaemia), talazoparib/placebo 11%, enzalutamide
Control arm	9%, olaparib/placebo 9%, abiraterone acetate	5.7%	12%, talazoparib/placebo 11%, enzalutamide
Treatment efficacy			
Primary endpoint	rPFS according to investigator assessment	rPFS according to blinded independent central review	rPFS according to blinded independent central review
Key secondary endpoint/s	OS	OS Time to cytotoxic chemotherapy Time to symptomatic progression	OS
Median rPFS in allcomers, months HR (95% CI, *p*-value)	24.8 vs 16.6 0.66 (0.54–0.81, $p<0.001$)	NA NA	NR vs 21.9 0.63 (0.51–0.78, $p<0.0001$)
Median rPFS in *BRCA* patients, months HR (95% CI, *p*-value)	NR vs 8.4 0.23 (0.12–0.43)	19.5 vs 10.9 0.55 (0.39–0.78, $p=0.0007$)	NR vs 11 0.20 (0.11–0.36, $p<0.00021$)
Median rPFS in HRRm patients, months HR (95% CI, *p*-value)	NR vs 13.9 0.50 (0.34–0.73)	16.7 vs 13.7 0.76 (0.60–0.97, $p=0.028$)	NR to 13.8 0.45 (0.33–0.61, $p<0.0001$)
Median rPFS in non-HRRm patients, months HR (95% CI, *p*-value)	24.1 vs 19.0 0.76 (0.60–0.97)	NA 1.09 (0.75–1.57, $p=0.66$)	NR vs 22.5 0.7 (0.54–0.89, $p=0.0039$)
Median OS in allcomers, months HR (95% CI, *p*-value)	42.1 vs 34.7 0.81 (0.67–1.00, $p=0.054$)	NA NA	NA 0.89 (0.69–1.14, $p=0.35$)
Median OS in *BRCA* patients, months HR (95% CI, *p*-value)	NR vs 23.0 0.29 (0.14–0.56)	30.4 vs 28.6 0.79 (0.55–1.12, $p=0.1828$)	NA 0.61 (0.31–1.23, $p=0.16$)
Median OS in HRRm patients, months HR (95% CI, *p*-value)	NR vs 28.5 0.66 (0.45–0.95)	29.3 vs 32.2 1.01 (0.75–1.36, $p=0.95$) IPCW 0.70 (0.49–0.99, $p=0.0414$)	NR vs 33.7 0.69 (0.46–1.03, $p=0.07$)
Median OS in non-HRRm patients, months HR (95% CI, *p*-value)	42.1 vs 38.9 0.89 (0.70–1.14)	NA NA	NA NA
Regulatory approvals			
US FDA	First-line treatment for *BRCA*-mutant mCRPC	First-line treatment for *BRCA*-mutant mCRPC	First-line treatment for HRRm mCRPC
EMA	All patients with mCRPC for whom chemotherapy is not clinically indicated	Not approved	All patients with mCRPC for whom chemotherapy is not clinically indicated

1L first-line, *AE* adverse event, *ARPI* androgen receptor pathway inhibitor, *BD* twice daily, *CI* confidence interval, *ECOG* Eastern Cooperative Oncology Group Performance Status, *EMA* European Medicines Agency, *FDA* Food and Drug Administration, *HR* hazard ratio, *HRR* homologous recombination repair, *IPCW* inverse probability censoring weighting, *mCRPC* metastatic castration-resistant prostate cancer, *mHSPC* metastatic hormone-sensitive prostate cancer, *NR* not reached, *OS* overall survival, *rPFS* radiographic progression-free survival

in both cohorts for the combination (*BRCA1/2* cohort: HR 0.54, [95% CI 0.33–0.90], $p=0.0181$; HRRm cohort: HR 0.70 [95% CI 0.49–0.99], $p=0.0414$) [56]. The final analysis with mature OS (unadjusted) after a median follow-up of 35.9 months focussed only on the *BRCA1/2* cohort, and demonstrated a modest OS benefit favouring the experimental arm (30.4 vs 28.6 months, HR 0.79 [95% CI 0.55–1.12], $p=0.1828$) [57]. These OS results are in contrast to the PROpel study, and potentially may be impacted by the subset (23.6% in experimental arm and 22.7% in the control arm) of patients in the experimental arm (HRRm population) who had received up to 4 months of abiraterone acetate before randomisation. Toxicity was higher in the experimental arm (frequency of grade ≥ 3 adverse events 72.2% vs 49.3%), with the most common ≥ grade 3 adverse events being anaemia (30.2% vs 8.5%) and hypertension (15.6% vs 12.3%). Following these results, the FDA approved the combination of niraparib and abiraterone acetate with prednisolone as first-line therapy for patients with *BRCA*-mutant mCRPC [58].

Third, the phase III TALAPRO-2 trial evaluated the combination of talazoparib with enzalutamide as a first-line treatment for patients with mCRPC [59, 60]. Patients were enrolled sequentially into two cohorts, the first being the HRR-unselected cohort (all-comers population), which included 169 patients with a HRR mutation and 636 without a known mutation. The second cohort selected for patients with an identified HRR mutation ($n=230$), to form a combined cohort of 399 patients with HRRm mCRPC. Eligible patients could have had prior exposure to docetaxel and abiraterone acetate in the mHSPC setting. Patients underwent prospective testing for HRR mutation status (see Table 1 for genes tested) and were randomised 1:1 into the experimental or control arm. Stratification occurred according to HRR status (HRRm vs non-HRRm vs unknown) as well as prior exposure to docetaxel or abiraterone acetate in the mHSPC setting. The primary endpoint was rPFS according to a blinded independent central review (in both all-comers and in the HRRm cohort), with OS a key secondary endpoint. At the planned primary analysis of the all-comers cohort, the median rPFS was not yet reached in the experimental arm for the intention-to-treat cohort, with a clear trend favouring the combination (NR vs 21.9 months, HR 0.63 [95% CI 0.51–0.78], $p=<0.0001$), suggesting that the combination confers a clinically meaningful benefit regardless of HRR status [59]. The recent analysis of the combined HRRm cohort ($n=399$) after a median follow-up of 17.5 and 16.8 months in the experimental and control arms, respectively, demonstrated that the combination arm had longer rPFS (NR vs 13.8 months, HR 0.45 [95% CI 0.33–0.61], $p<0.0001$) [60]. The OS data remains immature, with a trend in favour of the combination (HRRm cohort: HR 0.69 [95% CI 0.46–1.03], $p=0.07$; *BRCA* mutant cohort: HR 0.61 [95% CI 0.31–1.23], $p=0.16$]).

Importantly, in the all-comers intention-to-treat cohort, 28% and 38% had an undetermined HRR or *BRCA* mutation status, respectively. A post hoc analysis of the *BRCA* and HRRm subgroups attempted to explore whether the high proportion of 'undetermined' patients may in fact be unidentified biomarker-positive patients and, therefore, potentially contribute to the overall benefit seen in the intention-to-treat cohort [61]. For the *BRCA1/2* mutated cohort (10% of the intention-to-treat population), a clear benefit was seen in the experimental arm for both rPFS and OS (HR 0.24 [95% CI 0.12–0.49] and HR 0.53 [95% CI 0.28–1.03], respectively). Similar results were seen in the HRRm subgroup (HRs 0.51 [95% CI 0.36–0.72] and 0.68 [95% CI 0.47–0.99], respectively). Notably, an rPFS benefit was also seen in the non-*BRCA1/2* mutated cohort (median 33.1 vs 22.1 months, HR 0.71 [95% CI 0.52–0.96]) and non-HRRm cohort (NR-22.1 months, HR 0.69 [95% CI 0.49–0.98]). An OS trend favouring the experimental arm was also seen in both the non-*BRCA1/2* mutated and non-HRRm cohorts (HRs 0.76 [95% CI 0.56–1.03] and 0.88 [95% CI 0.63–1.23], respectively). For the *BRCA1/2* and HRR undetermined cohort, the magnitude of benefit appeared smaller (higher HRs) than the *BRCA1/2* mutated and HRRm cohorts, as well as the non-*BRCA1/2* and non-HRRm cohorts (undetermined *BRCA1/2* median rPFS NR-27.3 months, HR 0.75 [95% CI 0.53–1.07], undetermined HRRm median rPFS NR to 27.3 months, HR 0.73 [95% CI 0.47–1.13]). This analysis provides some reassurance that the inclusion of the 'undetermined' cohort in the non-*BRCA1/2* mutated and non-HRRm population in the intention-to-treat analysis did not significantly impact results, and falsely augment the survival benefit seen in the all-comers cohort [61]. Adverse events occurred more frequently in the experimental arm (≥ grade 3 adverse events 75% vs 45%). Anaemia was again the most common adverse event and most common cause for a dose reduction, occurring in 66% of the experimental arm compared with 17% in the control arm. Following this study, the FDA approved the combination of talazoparib and enzalutamide as first-line treatment for HRRm mCRPC [62]. The combination has also recently been approved by the European Medicines Agency for use in all patients with mCRPC in whom chemotherapy is not indicated [63].

A pooled analysis of multiple trials evaluating PARPis as first-line therapy for patients with HRRm mCRPC was performed by the FDA [64]. This study analysed individual patient data from the PROfound, PROpel, MAGNITUDE, TALAPRO-1, TALAPRO-2 and TRITON-2 trials. Differential results were observed by specific gene, with treatment benefit appearing greatest with *BRCA1*, *BRCA2*, *CDK12* and *PALB2* mutations, and an apparent lack of benefit seen in *CHEK2* and *ATM* mutations. In terms of ARPI-PARPi combinations,

a meta-analysis of the PROpel, MAGNITUDE and TALAPRO-2 trials confirmed a clear hierarchy of benefit based on HRR mutation status [65]. Pooled results for the shared primary endpoint of rPFS found a 35% rPFS improvement in the all-comer population (HR 0.65, 95% CI 0.56–0.76, $p<0.001$), with a differential magnitude of benefit depending on the subgroup by HRR status. The greatest rPFS benefit was seen in the *BRCA1/2* mutated cohort (HR 0.32, 95% CI 0.17–0.61, $p<0.001$), followed by the HRRm cohort (HR 0.55, 95% CI 0.39–0.77, $p<0.001$), and non-HRRm (HR 0.74, 95% CI 0.61–0.90, $p=0.003$). Toxicity was increased in the combination arm across the three studies, with a 45% increase in the relative risk of ≥ grade 3 treatment-related adverse events, in particular for ≥ grade 3 anaemia (31.9% vs 4.9%).

There is robust evidence supporting the use of an ARPI-PARPi combination in the *BRCA1/2* mutated subgroup, and treatment intensification should be considered in these patients. A benefit is also seen in the HRRm patient population, though differential responses occur depending on the specific gene mutation present. This is reflected in some of the regulatory approvals restricting use of an ARPI-PARPi combination to *BRCA*-mutated patients only. The benefit in the all-comers and non-HRRm populations is less clear, and needs to be balanced with the increased toxicity seen with combination therapy.

Several trials are ongoing that will further evaluate an ARPI-PARPi combination in mCRPC and hopefully clarify which patients or subgroup benefit from treatment intensification (see Table 2). In particular, the CASPAR trial (NCT04455750) is a randomised phase III study in which patients receive rucaparib versus placebo in combination with enzalutamide as first-line treatment for mCRPC. Patients are enrolled regardless of HRR mutational status. This is the only study incorporating both rPFS and OS as co-primary endpoints [66].

5 Method of HRR Mutation Status Testing

Tissue testing remains the gold standard currently for assessing HRR alterations in mCRPC. Although obtaining a fresh metastatic tumour biopsy is ideal, from a pragmatic point of view sampling bone metastases or deep intra-abdominal/pelvic lymph node metastases can be challenging. As a result, archival tissue is typically used to identify HRR alterations and, in most pivotal trials of PARPi in mCRPC, was used for molecular testing. At the same time, the use of archival tissue can be limited by DNA degradation, given that it is often many years old and may not be representative of the metastatic clone [67, 68]. There is increasing awareness of the role that testing plasma ctDNA may play in identifying HRR aberrations. Although reliable detection of biallelic gene inactivation in the setting of low ctDNA fraction is a limitation of ctDNA [69], an analysis from TALAPRO-2 showed high agreement (95%) between HRR status of tumour tissue and ctDNA [70]. Last, testing for germline-only HRR mutations can be performed using blood or saliva samples

A key difference across the PROpel, MAGNITUDE and TALAPRO-2 studies was the variation in the method of HRR mutational testing. The PROpel trial retrospectively analysed the HRR status of each patient after enrolment and randomisation had occurred, with the intention-to-treat cohort being HRR-unselected. Almost all patients (98%) provided samples of tumour tissue (mostly archival) and/or blood samples for ctDNA analysis, and blood germline samples. The HRR mutation status was determined using tumour tissue for 68% of patients [71]. In contrast, the MAGNITUDE and TALAPRO-2 studies both prospectively analysed the HRR status prior to randomisation and used tissue samples in 69% and 100% of patients, respectively (in addition to ctDNA for some patients) [59, 70, 72]. The range of HRR-related genes tested in each study also varied (see Table 1). All studies utilised the FoundationOne®CDx panel for tumour tissue analysis, though the key HRR-related genes included as part of each trial varied. *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *CDK12* and *CHEK2* mutations were included in the HRRm cohort of all three studies, while inclusion of genes in the *RAD* and *FANC* families was heterogeneous. This leads to lingering questions about whether patients harbouring these mutations benefit from combination therapy. Moving forwards, prospective studies should ideally include a consistent and wider range of HRR-related genes to provide further clarification on who derives benefit from combination ARPI-PARPi therapy.

6 Choice of ARPI and PARPi: Does it Matter?

Several key differences exist between these three trials that may contribute to the heterogeneity in outcomes. The most obvious difference is the variation in drugs utilised. Both PROpel and MAGNITUDE used abiraterone acetate as the ARPI, whilst TALAPRO-2 used enzalutamide. Enzalutamide, as an AR antagonist (along with darolutamide and apalutamide), competitively inhibits androgen binding to the AR whilst also preventing translocation of the androgen-AR complex to the nucleus, and, therefore, inhibits transcription of downstream proliferative and cell survival pathways [73, 74]. In contrast, abiraterone acetate is an androgen biosynthesis inhibitor via irreversible inhibition of 17α-hydroxylase/C17,20-lyase (CYP17). Inhibition of CYP17 enzymes prevents testosterone synthesis, and thereby also reduces downstream transcription pathways of the AR due to androgen suppression [75]. A subset of DNA repair genes are under transcriptional control of the AR (including

Table 2 Ongoing trials evaluating ARPI and PARPi in combination in mCRPC

Clinical trial number	Phase	Sponsor	Population	Treatment arms	HRR mutational status	Primary endpoint/s
CASPAR NCT04455750 [66]	III	Alliance for Clinical Trials in Oncology	First-line mCRPC (docetaxel or ARPI treatment allowed in mHSPC or nmCRPC)	*Experimental arm*: Rucaparib 600 mg BD + enzalutamide 160 mg daily *Control arm*: placebo + enzalutamide 160 mg daily	Unselected	rPFS and OS
FUZUPRO NCT04691804	III	Jiangsu HengRui Medicine Co., Ltd	First-line mCRPC	*Experimental arm*: fuzuloparib 150 mg BD + abiraterone acetate 1000 mg daily + prednisolone 5 mg BD *Control arm*: placebo + abiraterone acetate 1000 mg daily + prednisolone 5 mg BD	*Cohort 1*: Unselected *Cohort 2*: Selected	rPFS
NCT04108247	I	Jiangsu HengRui Medicine Co., Ltd	mCRPC, with 4 weeks of washout of any anti-tumour therapy	Fuzuloparib + abiraterone acetate 1000 mg daily + prednisolone 5 mg BD	Unselected	Incidence of AE and PK characteristics
PETRANHA NCT05367440	I/II	AstraZeneca	First-line or second-line mCRPC (trial also has a mHSPC arm)	Saruparib daily (in dose escalation) + physician's choice ARPI (enzalutamide, darolutamide, abiraterone acetate)	Unselected	Incidence of AEs/SAEs, RP2D/DLTs
NCT05405439	Ib/II	Chia Tai Tianqing Pharmaceutical Group Co., Ltd	mCRPC (no prior ARPI allowed in mHSPC or nmCRPC)	TQB3823 + abiraterone acetate 1000 mg daily + prednisolone 5 mg BD	Unselected	DLT, RP2D, rPFS

AE adverse event, *DLT* dose-limiting toxicity, *mCRPC* metastatic castration-resistant prostate cancer, *mHSPC* metastatic hormone sensitive prostate cancer, *nmCRPC* non-metastatic castration-resistant prostate cancer, *rPFS* radiographic progression-free survival, *OS* overall survival, *PK* pharmacokinetic, *RP2D* recommended phase II dose, *SAE* serious adverse event

BRCA1, and genes from *RAD* and *FANC* families), so it follows that inhibition of the AR results in transcriptional downregulation of key HRR genes, inducing a consequent functional 'HRR deficient' phenotype [39, 76]. Whilst preclinical data are only available for enzalutamide to the best of our knowledge, it can be assumed that the same synergistic effect is seen with abiraterone acetate [38, 39]. The choice of ARPI therefore is not likely to impact the interaction with a PARPi, though differences in pharmacokinetics, drug interactions and toxicity must also be considered.

Conversely, the choice of PARPi is likely more impactful on outcomes given the variation in the degree of PARP1 and PARP2 inhibition, PARP trapping, drug interactions and toxicity (see Table 3). The inhibition constant (K_I) for PARP1 is highest for talazoparib, followed by olaparib and then niraparib [77]. PARP2, in particular, is thought to have a crucial role in erythropoiesis [78], and therefore, potent enzyme inhibition may be a key driver of anaemia [79]. For PARP2, both olaparib and talazoparib exert a similar degree of inhibition (median 0.2 nM), with niraparib again the least potent PARPi. In vivo data suggest that talazoparib has the greatest potency in both *BRCA*− and *BRCA*+ cell lines [77]. All PARPi bind to the catalytic domain of PARP1 protein, resulting in interruption of the ADP-ribosylation process and trapping of PARP1 within chromatin. The strength of PARP1 trapping varies across different PARPi owing to differing molecular structures [80]. Talazoparib has the most potent PARP1 trapping capacity when compared to olaparib and niraparib [81]. In vitro data suggest the cytotoxicity resulting from PARP1 trapping leads to greater radiosensitisation, though there are no convincing data that this translates to increased efficacy when used in monotherapy and may lead to increased toxicity [81, 82]. Consequently, the highest incidence of ≥ grade 3 toxicity has been observed with talazoparib when combined with enzalutamide, and this study had the highest incidence of treatment discontinuation (see Table 1).

Importantly, the dose of PARPi when combined with an ARPI in some cases is reduced compared with the standard monotherapy dose. In the MAGNITUDE trial, niraparib 200 mg daily was administered in combination with abiraterone acetate compared to the standard monotherapy dose of 300 mg daily. This was because of an earlier phase Ib trial demonstrating increased toxicity when niraparib 300 mg daily was combined with either apalutamide 240 mg daily or abiraterone acetate 1000 mg with prednisolone 10 mg daily, and consequently, the recommended phase II dose when combined with abiraterone acetate was 200 mg daily[83]. The impact of this dose reduction may have compromised drug potency and therefore efficacy. In this study, niraparib exposures were lower in combination with apalutamide compared with when used alone. This was hypothesised to be due to apalutamide inducing the metabolism of niraparib via a drug–drug interaction. This effect was not seen when combined with abiraterone acetate, with niraparib exposure being dose proportional and in

Table 3 Comparison of PARPi used in metastatic castration-resistant prostate cancer in combination with an ARPI

	Olaparib	Niraparib	Talazoparib
Relative PARP1 trapping capacity	++	++	+++
Single-agent dose	300 mg PO BD	300 mg PO daily	1 mg PO daily
Dose when combined with ARPI	300 mg PO BD (abiraterone acetate)	200 mg PO daily (abiraterone acetate)	0.5 mg PO daily (enzalutamide)
IC_{50} [85]	PARP1: 1–19 nM PARP2: 1–251 nM	PARP1: 2–35 nM PARP2: 2–15.3 nM	PARP1: 0.6–1.1 nM PARP2: 4.1 nM
Elimination half-life (hours)	15	48-51	90
Any AE ≥ grade 3 (as monotherapy)	51% (30)	75% (29)	48% (28)
Any AE ≥ grade 3 (combined with ARPI)	56% (49)	72% (55)	75% (59)
≥ Grade 3 anaemia	16%	30%	46%
≥ Grade 3 toxicities (from most common)	Anaemia, venous thromboembolic events, hypertension, fatigue	Anaemia, hypertension, thrombocytopaenia, fatigue	Anaemia, neutropaenia, hypertension, thrombocytopaenia
Metabolism	Uses primarily CYP3A for metabolism	By carboxylesterases to inactive metabolite	Minimal hepatic metabolism
Drug interactions and considerations	Caution when using moderate/strong CYP3A inducers/inhibitors	Induces CYP1A2 (caution recommended for drugs that are CYP1A2 substrates)	P-glycoprotein inhibitors may increase talazoparib exposure Strong P-glycoprotein inducers should be avoided

AE adverse event, *ARPI* androgen receptor pathway inhibitor, *BD* twice daily, *CYP* cytochrome P450, *IC_{50}* half-maximal inhibitory concentration, *PARP1* poly(ADP-ribose) polymerase 1, *PARP2* poly(ADP-ribose) polymerase 2, *PO* oral

keeping with previous data for monotherapy exposure. Similarly, a lower dose of talazoparib (0.5 mg daily compared to 1 mg daily) was administered in TALAPRO-2 when combined with enzalutamide. This was based on a run-in study to TALAPRO-2 that identified a drug–drug interaction that resulted in a similar steady state of talazoparib exposure with 0.5 mg daily as seen with 1 mg daily when used as monotherapy [84].

7 Where Should We Sequence the ARPI-PARPi Combination in the Evolving Landscape of Metastatic Prostate Cancer?

Since the PROpel, MAGNITUDE and TALAPRO-2 trials commenced patient recruitment, there have been significant advances and changes made to the treatment landscape for prostate cancer. An ARPI in combination with ADT is now considered standard-of-care treatment for mHSPC. This complicates the interpretation of such first-line mCRPC studies, with the majority of patients in these studies being ARPI naïve prior to enrolment. Considering the efficacy of an ARPI switch is generally low [86], the impact of a prior ARPI on the efficacy of a subsequent ARPI-PARPi combination is an important question. The MAGNITUDE and TALAPRO-2 trials both allowed a prior alternate ARPI if given in the mHSPC setting. In the MAGNITUDE study, only a minority of patients had received an alternate ARPI for either mHSPC or nmCRPC (eight and five patients in each arm). In these subgroups, the median rPFS favoured the niraparib arm in both the HRRm and *BRCA1/2* cohorts, though data are limited by very small numbers (HRRm cohort: not evaluable vs 4.3 months, HR 0.19 [95% CI 0.03–1.23]; *BRCA1/2* cohort: not evaluable vs 4.3 months, HR 0.11 [95% CI 0.01–1.12]). In TALAPRO-2, 16 patients in the HRRm intention-to-treat cohort had received prior abiraterone acetate in both the experimental and the placebo arms. A subgroup analysis for rPFS reported outcomes for patients based on prior treatment/s and found that the benefit of talazoparib was maintained regardless of prior abiraterone acetate or docetaxel (HR 0.43 [95% CI 0.26–0.70]). Outcomes for patients who received prior abiraterone acetate were not independently reported. In the PROpel trial, only one patient received a prior ARPI for mHSPC. It is difficult to extrapolate from these data whether the ARPI-PARPi combination following progression on a prior ARPI remains an efficacious therapeutic option. The ongoing CASPAR and FUZUPRO trials may provide further insights given they both allow prior ARPI for mHSPC (see Table 2) [66].

Differential responses to treatment have previously been reported in prostate cancer depending on whether the treatment is sequenced before or after taxane chemotherapy. Between 20% and 23% of patients in the PROpel, MAGNITUDE and TALAPRO-2 trials had received prior docetaxel for mHSPC, and all trials stratified patients based on prior taxane exposure. In terms of rPFS, patients in the PROpel intention-to-treat population derived a similar benefit from the experimental arm regardless of prior docetaxel (HR 0.61 in the post-docetaxel cohort [95% CI 0.40–0.92], compared to HR 0.71 [95% CI 0.56–0.89] for docetaxel naïve patients). Similar outcomes were seen in the intention-to-treat population for OS (HR 0.76 in the post-docetaxel group [95% CI 0.52–1.11] vs HR 0.85 for the docetaxel-naïve group [95% CI 0.67–1.07]) [49]. In TALAPRO-2, a subgroup analysis for the post-docetaxel cohort specifically was not available in the all-comer intention-to-treat cohort. The HR for median rPFS for HRRm patients was similar in the overall (0.45 [95% CI 0.33–0.61]) and post-docetaxel (0.46 [0.31–0.69]) cohorts [60]. In the MAGNITUDE trial, however, the extent of benefit in terms of median rPFS was higher for HRRm patients who were taxane naïve (16.6 vs 13.8 months, HR 0.71 [95% CI 0.53–0.96]) compared with those who had received prior docetaxel (13.4 months vs 10.9 months in the placebo arm, HR 0.89 [95% CI 0.48–1.66]). Further, for the *BRCA1/2* subgroup, patients who had received prior docetaxel did not appear to benefit from the experimental arm (median rPFS for post-docetaxel subgroup 13.4 months vs 13.7 months, HR 0.98 [95% CI 0.48–2.02]). For the taxane-naïve subgroup, median rPFS favoured the experimental arm (22.2 vs 10.9 months, HR 0.47 [95% CI 0.31–0.69]). These results suggest that HRRm patients may derive a greater benefit from the ARPI-PARPi combination if given *prior* to chemotherapy, particularly for patients harbouring a *BRCA1/2* mutation. It is important to note that though these studies stratified outcomes based on prior docetaxel, they were not powered to analyse the pre-docetaxel and post-docetaxel cohorts as an endpoint. Further, in all three aforementioned studies, docetaxel was given for mHSPC, which typically is a limited course of up to six cycles, and often ceased before treatment resistance occurs. Importantly, TRITON-2 is the only trial to directly compare a PARPi to docetaxel given in the mCRPC setting. Data from both the PROfound and TRITON-2 studies support the use of PARPi monotherapy before docetaxel chemotherapy after progression on an ARPI for patients with a *BRCA1/2* mutation [33, 34]. Further investigation with prospective studies is needed to answer the question of optimal

Table 4 Ongoing trials evaluating ARPI and PARPi in combination in mHSPC

Clinical trial number	Phase	Population	Treatment arms	HRR mutational status	Primary endpoint
AMPLITUDE NCT04497844 [87]	III	First-line mHSPC	*Experimental arm*: niraparib 200 mg daily + abiraterone acetate 1000 mg daily + prednisolone 5 mg daily *Control arm*: placebo + abiraterone acetate 1000 mg daily + prednisolone 5 mg daily	Selected	rPFS
TALAPRO-3 NCT04821622 [88]	III	First-line mHSPC	*Experimental arm*: talazoparib 0.5 mg daily + enzalutamide 160 mg daily *Control arm*: placebo + enzalutamide 160 mg daily	Selected	rPFS
NCT05167175 [96]	II	First-line mHSPC	Olaparib 300 mg BD + abiraterone acetate 1000 mg daily + prednisolone 5 mg daily	Selected	rPFS
EvoPAR-Prostate01 NCT06120491	III	First-line mHSPC	*Experimental arm*: saruparib + physician's choice ARPI (abiraterone acetate, darolutamide or enzalutamide) *Control arm*: placebo + physician's choice ARPI (abiraterone acetate, darolutamide or enzalutamide)	Selected	rPFS
NCT04734730 [89]	II	First-line mHSPC	Talazoparib 1 mg daily + abiraterone acetate 1000 mg daily + prednisolone 5 mg BD	Unselected	PSA nadir < 0.2
ZZ First Trial NCT04332744 [90]	II	First-line mHSPC	*Experimental arm*: talazoparib 0.5 mg daily + enzalutamide 160 mg daily *Control arm*: placebo + enzalutamide 160 mg daily	Unselected	PSA-CR

PFS radiographic progression free survival, PSA prostate-specific antigen, PSA-CR PSA complete response (PSA <0.2 ng/mL)

treatment sequencing of an ARPI-PARPi combination with regard to docetaxel given in the mCRPC setting.

8 Future Perspectives

Early treatment intensification remains a key focus in the management of advanced prostate cancer, with a shift towards implementing combination therapies at diagnosis of metastatic disease. As such, ARPI-PARPi combinations are now being studied in the mHSPC setting (see Table 4). In particular, the AMPLITUDE trial (NCT04497844) [87] is evaluating whether the combination of niraparib with abiraterone acetate improves rPFS in HRR-selected patients. TALAPRO-3 (NCT04821622) [88] follows on from TALAPRO-2 and explores the same combination in a HRR-selected mHSPC cohort. Importantly, two phase II trials are evaluating the combination of talazoparib with an ARPI in HRR-*un*selected mHSPC cohorts (NCT04734730, NCT04332744) [89, 90]. These studies will assist with identifying which patients or subgroups derive benefit from the combination treatment in an earlier setting.

Moreover, the development of selective PARP1 inhibitors may overcome the haematological toxicity that is thought to result predominantly from PARP2 inhibition, thereby potentially allowing dosing that results in greater PARP1 inhibition and improved efficacy while also improving drug tolerability. High-grade anaemia was the most common adverse effect in the PROpel, MAGNITUDE, and TALAPRO-2 trials, and resulted in PARPi dose reductions or discontinuation in some cases. Both PARP1 and PARP2 bind to sites of DNA damage, and olaparib, niraparib and talazoparib inhibit both enzymes to varying degrees. The mechanism resulting in synthetic lethality in HRR-deficient cells, however, is thought to be reliant solely on the loss of PARP1 activity [91, 92]. Next-generation PARPis that selectively inhibit and trap PARP1, therefore, have become an area of interest, with several currently in development. Saruparib (AZD5305) is a first-in-class selective inhibitor and trapper of PARP1, and demonstrated minimal haematological toxicity in pre-clinical models [93]. It has been

evaluated in the phase I/IIa PETRA trial (NCT04644068) in multiple HRRm tumour types and demonstrated promising clinical activity with favourable tolerability [94]. Saruparib in combination with an ARPI in metastatic prostate cancer was shown to be well tolerated in the PETRANHA trial [95], and continues to be evaluated in the phase III EvoPAR-Prostate01 (NCT06120491) trial in both HRRm and non-HRRm cohorts.

9 Conclusions

Concurrent inhibition of AR and PARP with an ARPI-PARPi combination in patients with mCRPC leads to therapeutic lethal synergy due to several mechanisms. This translates to improved survival outcomes for some patients, as demonstrated by three pivotal, phase III randomised trials evaluating ARPI-PARPi combinations as first-line treatment for mCRPC. A hierarchy of benefit is evident, with patients harbouring a *BRCA* mutation gaining the most benefit from an ARPI-PARPi combination, followed by other selected pathogenic HRR mutations, and last, HRR-unselected patients or non-HRRm patients deriving the lowest magnitude of benefit. Given these differential responses, and the potential impact of prior docetaxel on efficacy, early screening for HRR mutations is crucial to guide treatment choices. Because of the rapidly changing treatment landscape for advanced prostate cancer, and the expectation that most patients will now receive an ARPI for mHSPC, the interpretation of studies such as PROpel, MAGNITUDE, and TALAPRO-2 is not straightforward. As more selective PARPis are developed and with several trials underway in both HRR-selected and HRR-unselected populations in mHSPC, we will hopefully gain further insights into the benefits of ARPI-PARPi combinations in prostate cancer. Identification of patients and subgroups who derive greatest benefit from treatment intensification will guide the treatment paradigm moving forwards.

Declarations

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Authors' Contributions LK wrote the initial draft of the manuscript. AA and BT reviewed and edited the manuscript. AA provided manuscript oversight.

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