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Development of PARP inhibitors in advanced prostate cancer

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***Abstract*:** The relatively high prevalence of alterations in the homologous recombination repair (HRR) pathway described in advanced prostate cancer provides a unique opportunity to develop therapeutic strategies that take advantage of the decreased tumor ability to repair DNA damage. Poly ADP-ribose polymerase (PARP) inhibitors have been demonstrated to improve the outcomes of metastatic castration-resistant prostate cancer (mCRPC) patients with HRR defects, particularly in those with *BRCA1/2* alterations. To expand the benefit of PARPi to patients without detectable HRR alterations, multiple studies are addressing potential synergies between PARP inhibition (PARPi) and androgen receptor pathway inhibitors (ARSi), radiation, radioligand therapy, chemotherapy, or immunotherapy, and these strategies are also being evaluated in the hormone-sensitive setting. In this review, we summarize the development of PARPi in prostate cancer, the potential synergies, and combinations being investigated as well as the future directions of PARPi for the management of the disease.

Plain language summary

Development of PARP inhibitors in advanced prostate cancer

Alterations in the mechanisms responsible for repairing damaged DNA are frequently altered in advanced prostate cancer. This provides a unique opportunity to develop therapies that exploit the decreased ability of these prostate tumours to repair DNA. Poly ADP-ribose polymerase (PARP) inhibitors have been successfully used to treat other tumor types with similar deficiencies and recently, multiple studies have demonstrated its efficacy also in prostate cancer, particularly in tumors with BRCA1/2 alterations. To expand the benefit of PARPi to patients without detectable DNA repair alterations, multiple studies are addressing potential synergies between PARP inhibition (PARPi) and androgen receptor pathway inhibitors (ARSi), radiation, radiopharmaceuticals, chemotherapy and immunotherapy in different disease stages. In this review, we summarize the development of PARPi in prostate cancer, the potential synergies and combinations being evaluated as well as the future directions of PARPi for the management of the disease.

Keywords: BRCA, HRR, niraprib, olaparib, PARP inhibition, prostate cancer, rucaparib, talazoparib

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Introduction

Prostate cancer is the second most frequent cancer and the fifth leading cause of cancer-related deaths in men globally.[1] Androgen deprivation therapy (ADT) remains the cornerstone of management for advanced prostate cancer; nonetheless, the

addition of a variety of therapies to ADT including taxane-based chemotherapy (docetaxel and cabazitaxel), androgen receptor signaling inhibitors (ARSi, abiraterone, enzalutamide, darolutamide, and apalutamide), and radiopharmaceuticals (radium^{223} and lutetium^{177}) have demonstrated to prolong the overall survival (OS) of these men.[2] However, response to these agents is heterogeneous and even those patients who achieve significant responses eventually become resistant. In consequence, the disease remains incurable, and new therapeutic strategies are needed.

In the last decade, multiple studies have described the molecular landscape of advanced prostate cancer and the mechanisms behind treatment resistance.[3–5] A better understanding of the molecular heterogeneity of the disease allows the search for new treatment options. Alterations in genes involved in the homologous recombination repair (HRR) pathway have been reported in a quarter of patients with advanced prostate cancer[3,6] and provide a unique opportunity to develop therapeutic strategies that take advantage of the decreased tumor ability to repair DNA damage. Poly ADP-ribose polymerase (PARP) inhibitors have been investigated in patients with metastatic castration-resistant prostate cancer (mCRPC) with HRR defects demonstrating great efficacy for the treatment of these tumors, particularly for those with BRCA1/2 alterations. Nonetheless, the role of PARP inhibitors (PARPi) is evolving as preclinical models suggest potential synergies with other agents, and these combinations are being evaluated in multiple clinical trials in mCRPC but also in the hormone-sensitive setting.

Prevalence and clinical implications of HRR alterations in prostate cancer

Alterations in DNA Damage Repair DDR genes have been observed in 10% of localized prostate tumors and almost a third of metastatic cases.[3,4] Among these genes, the HRR pathway is the most commonly impaired DNA repair pathway in prostate cancer. In 28% of the samples analyzed in the PROFound study, at least one HRR alteration was found. The most frequently altered gene was *BRCA2* (8.7%), followed by *CDK12* (6.3%), *ATM* (5.9%), *CHEK2* (1.2%), and *BRCA1* (1%). Co-occurring aberrations in two or more HRR genes were identified in 2.2% of cases.[6] Importantly, the analysis of paired samples from primary tumors and metastases at the time of castration resistance in various series has revealed no difference in the prevalence of DDR (and HRR) aberrations, suggesting that these events occur early in the progression of lethal prostate cancer.[5,7,8] Importantly, a significant proportion of HRR alterations found in tumors originates from the germline, including 50% of *BRCA2* mutations.[9,10]

Germline BRCA2 mutations are a well-established poor prognosis factor for localized[11–13] and advanced[14,15] prostate cancer. The role of concurrent genomic events is unclear but it seems that certain events (i.e. *RB1-BRCA2* co-deletion, *MYC* amplification) could modulate the effect of inherited BRCA2 mutations on patient outcomes.[16] A recent study suggests that somatic BRCA2 alterations would have a negative prognostic impact on mCRPC patients conventionally treated with ARSi and taxanes.[17] The clinical implications of other HRR genes are not well established except for biallelic CDK12 inactivation,[18,19] consistently reported to also have a detrimental effect. Inactivating *CDK12* mutations leads to gene fusion-induced neoantigens and a potential sensitivity to immunotherapy that is being addressed in several studies.[19]

Mechanism of action of Poly (ADP-Ribose) polymerase inhibitors

Poly (ADP-ribose) polymerases (PARP) is a family of ADP-ribosyl transferase enzymes, of which PARP1 is the most abundant, that transfer negatively charged poly ADP-ribose (PAR) groups from donor NAD^+ molecules onto their target proteins. Through these PAR chains, PARPs control a wide array of cellular processes, such as DNA repair, transcriptional regulation, and RNA interference among others.[20] PARP1 is a key component of the base excision repair mechanism that acts as a DNA damage sensor and a signal transducer. It detects single-strand breaks, binds to the DNA adjacent to the damage, and then synthesizes PAR chains on target proteins (PARylation) leading to the recruitment of additional factors that complete the DNA repair process. PARP1 autoPARylation leads to its own release for the site of DNA damage.[21,22]

Based on this critical role in initiating response to DNA damage, PARP has been an attractive pharmacological target for cancer therapeutics. PARP inhibitors (PARPi) mimic the structure of nicotinamide and have two general effects: catalytic inhibition of PARP1 (preventing PARylation) and

'trapping' PARP1 on damaged DNA. The precise mechanism explaining trapping is unclear but two possibilities have been proposed: autoPARylation inhibition prevents the release of PARP1 from DNA or PARPi binding to the catalytic site modifies PARP1 structure enhancing DNA avidity.[22,23] Then, trapped PARP1 stalls the progress of replication forks, that in normal cells would be repaired by HRR proteins but in HRR-deficient cells (i.e. due to *BRCA2* mutations) alternative error-prone DNA repair mechanisms, such as nonhomologous end-joining repair (NHEJ), are used, leading to catastrophic genomic instability and cell death.[24] Initial reports described that BRCA1$^{-/-}$ or BRCA2$^{-/-}$ cell lines displayed a 60- to 1000-fold greater sensitivity to olaparib and talazoparib precursors than BRCA+/+ cell lines. These observations have been replicated numerous times with other PARPi.[25]

Several PARPi have been developed that differ in their ability to inhibit its catalytic activity and trap PARP in damaged DNA complexes[23,25] and subsequently show different antitumor activity.[24] At the same time, increased PARP trapping has been associated with high myelosupression.[26] Most PARPi clinically developed have limited selectivity for PARP1 over PARP2, although preclinical data suggest that synthetic lethality with *BRCA½* mutations was caused solely by PARP1 inhibition.[23] PARP2 seems to play a major role in the survival of hematopoietic/stem progenitor cells and its inhibition could result in the hematological toxicity observed in the clinic.[27] Other common class-specific side effects include fatigue and gastrointestinal toxicity. The type, grade, or frequency of side effects do not seem to be associated with the presence of BRCA½ or other HRR alterations.

After a variable period, resistance to PARPi eventually occurs. Resistance mechanisms to these drugs are complex and include events that restore HRR function such as secondary mutations restoring the open reading frame of HRR genes; replication folk protection; point mutations in the DNA-binding domain of *PARP1*; and alterations in drug efflux pumps affecting drug pharmacokinetics, among others.[24,28]

Development of PARP inhibitors in prostate cancer

PARPi were initially developed for cancer treatment as radio and chemo-sensitizing drugs but early preclinical observations supported their development in monotherapy for BRCA-deficient tumors.[24] Germline BRCA1/2 mutation carriers with different tumor types were the initial target population to test the PARPi-BRCA synthetic lethal hypothesis in the clinic. A first-in-human clinical trial with KU-0059436 (a precursor of Olaparib) was conducted to determine safety, the adverse-event profile, establish a recommended dose, and the pharmacokinetic and pharmacodynamic profiles. Once these were established, the expansion cohorts included only cancer patients with germline BRCA mutations to test the hypothesis that patients with *BRCA*-related tumors would show an objective antitumor response to single-agent olaparib. Twelve of the 19 (63%) carriers with evaluable *BRCA*-related tumors achieved objective response or disease stabilization for ⩾4 months. One germline *BRCA2* mutation carrier with prostate cancer was included who benefited from the drug for over 2 years.[29]

The first-in-man clinical trial of niraparib (MK4827) included an exploratory expansion cohort of 18 mCRPC patients, in addition to 3 germline *BRCA* mutation carriers with CRPC recruited during the dose-escalation phase. Nine of those 21 mCPRC patients (43%) had stable disease for a median duration of 8.5 months; no radiological responses per RECIST were documented although one patient experienced a >50% decrease in prostate-specific antigen (PSA) on treatment, remaining on treatment for 10 months.

TOPARP-A[30] was a phase II trial to identify possible biomarkers that could help identify mCRPC patients who would benefit from treatment with olaparib. The study enrolled 50 molecularly unselected mCRPC heavily pretreated. The main objective was the composite response rate, defined either as objective response rate (ORR) by response evaluation criteria in solid tumors 1.1 (RECIST 1.1), a decline in PSA level of at least 50% (PSA50), and/or conversion in circulating tumor cell (CTC) count from ⩾5 cells/7.5 mL to <5 cells/7.5 mL of blood. Overall, 16/49 (32%) evaluable patients fulfilled the prespecified definition of response. These included 11/49 (22%) patients achieving at least 50% PSA fall and 6/32 (19%) patients with measurable disease in CT scan achieving a RECIST response. All patients donated fresh and/or archival tumor samples for molecular analysis, and next-generation targeted sequencing was pursued to investigate putative biomarkers of response. A patient was classified

as 'biomarker-positive' if a homozygous deletion or deleterious mutation was identified in any of the DNA repair genes analyzed. Almost all patients who responded to therapy (14/16) were biomarker positive, including seven patients harboring somatic or germline BRCA2 alterations that responded to olaparib. Other responding patients had alterations in *ATM, PALB2, CHEK2*, and other genes. Conversely, these genomic aberrations were uncommon in non-responding patients. Disease control lasted at least 6 months in many of these heavily pretreated cases, with four patients receiving the drug for over a year. These data led to a second stage of the trial (TOPARP-B[31]) in which patients were pre-selected based on the detection of tumor genomic aberrations associated with sensitivity to PARPi.

Further phase II trials have investigated the efficacy and safety of other PARPi in patients with HRR-altered mCRPC patients and disease progression to several treatment lines, with the primary endpoints being ORR and/or PSA50. TOPARP-B,[31] TRITON2,[32–34] TALAPRO-1,[35] and GALAHAD[36] have, respectively, assessed the efficacy of olaparib, rucaparib, talazoparib, and niraparib in patients with mCRPC who had progressed on prior ARSIs and taxanes. In all of them, a marked benefit was seen in the *BRCA 1/2* population, with ORR ranging from 34% to 52% and PSA response from 43% to 76%. The antitumor activity associated with alterations in non-BRCA HRR genes is heterogeneous; while the clinical benefit of PARPi in patients with *ATM, CDK12*, or *CHEK2* alterations seems to be limited at best,[31,32,35,36] relevant response rates have been reported in patients with *PALB2* alterations[31,33,35] (Table 1).

In light of these encouraging findings, the phase III trials PROfound and TRITON3 were developed (Table 2). PROfound[6,37] has been the first randomized phase III biomarker-driven trial in prostate cancer aimed to assess the potential benefits of olaparib (300 mg bid) compared to a second ARSi (enzalutamide or abiraterone) in patients with mCRPC who had disease progression after receiving a prior ARSi, either in the context of castration-naïve or castration-resistant disease. The primary endpoint was radiologic progression-free survival (rPFS) in cohort A and the overall population. A total of 4858 tissue samples from 4047 patients were tested for genomic alterations in *ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCl, PALB2, PPPR2A, RAD51B, RAD51C*, and *RAD54L*. Next-generation sequencing was successful in 58% of samples (69% of patients). Out of these, 28% (778 patients) had a qualifying deleterious alteration in at least one of the 15 prespecified genes. Finally, 387 patients m*et al*l the entry criteria and were enrolled in the trial. According to the identified mutation, patients were assigned to cohort A (*BRCA1, BRCA2*, or *ATM* alterations, $n = 245$) or cohort B (other genes assessed, $n = 142$). The frequency of mutations in cohort A was 13 (5%) in *BRCA1*, 127 (33%) in *BRCA2*, and 84 (21%) in *ATM*. Olaparib showed rPFS benefit, with an absolute increased survival of 3.8 months (HR 0.34, $p < 0.001$) in cohort A and 2.3 months (HR 0.49; 95%CI 0.38–0.63, $p < 0.001$) in the overall population. Olaparib also improved OS in cohort A (19.1 *versus* 14.7 months, HR 0.69, 95% CI 0.50–0.97) but not in cohort B (HR 0.96 95%CI 0.63–1.49). A benefit in OS was noted in the overall population (HR 0.79, 95% CI 0.61–1.03), mostly driven by patients in cohort A. Importantly, 66% of patients in the control arm crossed over to olaparib after progression and a sensitivity analysis adjusted for the crossover showed a 58% decrease in the risk of death for patients in cohort A. A gene-by-gene exploratory analysis suggested the greatest benefit from olaparib for *BRCA2*-altered patients and a less clear benefit for those with *ATM* alterations. The median duration of treatment was 7.6 months (0.03–29) in the olaparib group and 3.9 (0.6–29.1) in the control group. The most common adverse events related to olaparib were anemia (39%), nausea (36%), and fatigue/asthenia (32%). Olaparib was discontinued because of anemia in 7% of patients and because of neutropenia, thrombocytopenia, nausea, vomiting, or fatigue/asthenia in 1% of patients. One case of fatal acute myeloid leukemia was reported in a patient with a germline *BRCA2* mutation diagnosed 54 days after discontinuation of olaparib. In view of these results, the FDA-approved olaparib for patients with alterations in the HRR genes tested in the PROFound study while EMA restricted the approval only to patients with *BRCA1* and *BRCA2* alterations.

The TRITON-3 study[38] has assessed rucaparib monotherapy (600 mg bid) for the treatment of mCRPC patients with *BRCA1, BRCA2*, or *ATM* after progression to an ARSi. Of the 405 patients enrolled, 44 had alterations in *BRCA1*, 258 in *BRCA2* and 103 in *ATM*. Patients were

Table 1. Phase II studies have investigated the efficacy of PARP inhibitors in monotherapy for the treatment of mCRPC.

Study characteristics	TOPARP-B	TRITON2	TALAPRO-1	GALAHAD
Drug	Olaparib	Rucaparib	Talazoparib	Niraparib
Study design and population	Phase II, single arm mCRPC after taxanes (ARSi allowed) *N* = 98	Phase II, single arm mCRPC after ARSi and taxane *N* = 193	Phase II, single arm mCRPC ARSi and taxane *N* = 127	Phase II, single arm mCRPC ARSi and taxane *N* = 223
Primary objective	Composite endpoint: ORR, PSA50, CTC conversion	ORR in pts with DDR alterations	ORR in pts with DDR alterations	ORR in biallelic BRCA1/2
Results	Composite response (1ry endpoint) -By gene: 85% *BRCA1/2* 37% *ATM* 25% *CDK12* 57% *PALB2* 20% other -By dose cohort: 54% with 400 mg bid 39% with 300 mg bid	ORR (1ry endpoint) 43.5% *BRCA1/2* 10.5% *ATM* 11.1% *CHEK2* 0% *CDK12* 28.5% other DDR PSA50 (2ry endpoint) 54.8% BRCA1/2 4.1% ATM 16.7% CHEK2 6.7% CDK12 36% other DDR	ORR (1ry endpoint) 46% *BRCA 1/2* 25% *PALB2* 12% *ATM* 0% other DDR PSA50 (2ry endpoint) 66% *BRCA 1/2* 75% *PALB2* 7% *ATM* 6% other DDR	ORR (1ry and 2ry endpoint): 26% *BRCA1/2* 5% in non-BRCA DDR PSA50 (exploratory endpoint) 43% *BRCA1/2* 5% non-BRCA DDR
Specimen tested	Tumor tissue Central	Plasma or tumor tissue Central/local	Tumor tissue Central	Plasma or tumor tissue Central analysis
Test used	Targeted customized NGS panel	FoundationOne CDx®	FoundationOne CDx®	Resolution-HRD® FoundationOne CDx®
Genes screened	113 DDR genes	*ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, RAD54L*	*ATM, ATR, BRCA1, BRCA2, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C*	*ATM, BRCA1, BRCA2, BRIP1, CHEK2, FANCA, HDAC2, PALB2*
Genomic alt. required		Mono- and biallelic DDR alterations		Biallelic or germline DDR alt.

mCRPC, metastatic castration-resistant prostate cancer; NGS, Next generation sequencing; PSA, prostate-specific antigen.

randomized to receive rucaparib or a physician's choice (docetaxel or a second ARSi). At 62 months, the median rPFS in the intention-to-treat population was significantly longer in the rucaparib than in the control arm (10.2 months *versus* 6.4 months; HR 0.61, 95% CI 0.47–0.8). The difference in rPFS was driven by BRCA patients (11.2 months *versus* 6.4 months; HR 0.5, 95% CI 0.36–0.69) as no benefit was noted in the *ATM*-mutated population (8.1 *versus* 6.8 months; HR 0.95, 95% CI 0.59–1.52). TRITON-3 has provided the first direct comparison between a PARPi and docetaxel; in patients with BRCA1/2 alterations, treatment with rucaparib resulted in more prolonged rPFS (11.2 *versus* 8.3 months; HR 0.53 95% CI 0.37–0.77), while no difference was noted in *ATM* patients (8.1 *versus* 8.1 months, HR 1.1, 95% CI 0.57–2.11). In line with the PROfound study, compared to a second ARSi, rucaparib resulted in improved rPFS in patients with *BRCA* alterations (11.2 *versus* 4.5 months, HR 0.38, 95% CI 0.25–0.58) with less clear benefit in *ATM* patients (8.1 *versus* 5.7 months, HR 0.82, 95% CI 0.47–1.45). The most common adverse events related to rucaparib were fatigue (61%), nausea (50%), anemia (47%), and decreased appetite (36%). The most frequent grade ⩾3 toxicity were anemia (24%), neutropenia (7%), fatigue (7%), and thrombocytopenia (6%). No cases of myelodysplastic syndrome or

Table 2. Summary of phase III trials TRITON 3 and PROFOUND cohort A.

Study characteristics	TRITON 3		PROFOUND – COHORT A	
	Rucaparib (*n* = 270)	Physician's choice second ARPi (*n* = 60)	Olaparib (*n* = 162)	Physician's choice second ARPi (*n* = 83)
BRCA1	29 (11%)	9 (12%)	8 (5%)	5 (6%)
BRCA2	172 (64%)	51 (68%)	80 (49%)	47 (57%)
ATM	69 (26%)	15 (20%)	60 (37%)	24 (29%)
Median age, years (range)	70 (45–90)	72 (54–92)	68 (47–86)	67 (49–86)
ECOG PS 0, *n* (%)	132 (49%)	33 (55%)	84 (52%)	34 (41%)
Baseline PSA, ng/mL	27 (0.1–1247)	29 (0–1039)	62.2 (21.9–280.4)	112.9 (34.3–317.1)
Gleason score ⩾8, *n* (%)	173 (64%)	37 (62%)	105/157 (67%)	54/80 (67%)
Measurable disease at baseline	106 (39%)	21 (35%)	95 (59%)	46 (55%)
Visceral metastasis at baseline	74 (27%)	46 (34%)	49 (30%)	23 (28%)
Prior ARSi				
1	100%	100%	130 (80%)	69 (83%)
⩾2	0	0	32 (20%)	14 (17%)
Prior Taxanes				
1	63 (23%)*	16 (27%)*	76 (47%)	32 (39%)
⩾2	0	0	29 (18%)	20 (24%)
Imaging-based PFS	10.2 *versus* 4.5 months HR 0.47 (95%CI 0.34–0.66) $p < 0.0001$		7.39 *versus* 3.55 months HR 0.34 (95%CI 0.25–0.47) $p < 0.0001$	
Overall survival	23.6 *versus* 20.9 months[$] HR 0.94 (95% CI, 0.72–1.23)		19.1 *versus* 14.7 months HR 0.69 (95% CI 0.5–0.97) $p = 0.017$	

*Docetaxel for metastatic hormone-sensitive prostate cancer.
[$]Interim overall survival data reported with 59% data maturity.
PFS, progression-free survival; PSA, prostate-specific antigen.

acute myeloid leukemia have been reported. No mature OS data are still available. FDA has approved rucaparib for the treatment of *BRCA*-mutated mCRPC that has progressed to ARSi.

PARPi in combinations for the treatment of advanced prostate cancer

The role of PARPi in monotherapy to treat prostate tumors with alterations in *BRCA1, BRCA2*, and some other HRR genes has consistently been demonstrated in the studies mentioned above. Potential therapeutic synergies that could deepen response in these patients but may also expand the benefit of PARPi to a broader unselected population are now being addressed in multiple trials. Some studies are combining PARPi with other compounds that target *al*ternative DDR nodes (i.e. Wee1, HSP90, or ATR inhibitors) or induce DNA damage[39–41] (i.e. ^{177}Lutetium, ^{223} Radium) aiming to increase DNA damage during G1 and S phases of the cell cycle and to minimize repair during G2, leading to cell death. Combination with DNA-damaging chemotherapy[42] (i.e. carboplatin) would maximize the effect of DNA damage but is also challenging due to overlapping

toxicities. A second strategy consists of combining PARPi with drugs targeting other biological pathways that are modulated and/or to modulate HRR function, such as the PI3K/AKT pathway,[43] Vascular Endotelial Growth Factors (VEGFR),[44] and Androgen Receptor (AR) signaling[45–47] pathways. Finally, the rationale for developing combinations of PARPi and immunotherapy is that the genomic instability associated with HRR and other DDR defects may lead to neoantigen production and T-cell activation. Furthermore, the accumulation of cytosolic DNA may activate the innate immune system through the cGAS-STING pathway, inducing interferon-mediated response. This would subsequently lead to the activation of natural killer cells and macrophages and the infiltration, proliferation, and antitumor response of CD4 and CD8 T cells into the tumor. Paradoxically, the STING pathway and PARP inhibition also activate the expression of PD-L1.[48–50]

While most studies are still ongoing, the trials reported to date have shown limited antitumor activity from the combination of PARPi with cediranib,[44] pembrolizumab,[51] or nivolumab[52] in mCRPC patients without detectable HRR alterations and for those with HRR defects it is unclear whether the combinations add any benefit to PARPi in monotherapy. The most promising results have been reported from trials investigating the combination of PARPi with ARSi, with several lines of work showing a close interplay between the AR pathway and the DDR machinery, supporting the synergistic effect of ARSi and PARPi. It has been shown that AR transcriptionally stimulates the expression of a wide range of DNA repair genes, some of them through direct interaction of AR with AR binding sites in gene enhancer regions.[53,54] Prominent among the AR-regulated DDR genes seem to be those encoding components of the nonhomologous end-joining repair (NHEJ) but also genes involved in homologous recombination, mismatch repair, base excision repair, and the Fanconi anemia pathway. In line with these observations, Li *et al.*[55] reported that in both, AR-dependent and AR-independent cell lines, enzalutamide reduced the expression of a specific set of HR genes, including *BRCA1, RAD51C, RAD54L*, and *RMI2*, thus creating an HR deficiency and a *BRCA*-loss-like state (referred to as '*BRCA*ness'). Although AR inhibitor-induced '*BRCAness*' may be transient and shallow, a treatment strategy in which enzalutamide was followed by olaparib resulted in improved antitumoral activity in murine prostate cancer xenografts compared to monotherapy with either agent.[55] On the other hand, beyond its role in DNA damage repair, PARP1 has been suggested to be involved in the transcriptional control of AR[56] as its enzymatic activity is enhanced and required for AR function, tumor growth, and progression to castration resistance.[57] Based on this, early exposure to PARP inhibition might modulate AR signaling with downstream effects that maintain hormone-responsive disease for a longer period. Multiple interactions between the AR and HRR pathways have been reported although it remains unclear which of these mechanisms play a role in the synergy between ARSi and PARPi and whether there is inter- or intra- patient heterogeneity.

The potential synergy between ARSi and PARPi was tested by STUDY 8,[58] a phase II study that compared abiraterone with abiraterone plus olaparib in 142 mCRPC patients unselected for HRR alterations. The trial met its primary endpoint, with a median PFS of 13.8 months (95% CI 10.8–30.4) from the combination, compared with 8.2 months (95% CI 5.5–9.7, $p = 0.034$) in the control arm. No significant difference was observed in the secondary endpoint of OS, although the study may have been underpowered. Due to collection and testing issues, it was not possible to establish the presence of HRR alterations in a significant proportion of patients and there may be a disbalance of these genomic events between arms. A 25% increase in the incidence of grade 3–4 adverse events was noted in the combination arm, largely due to anemia, as well as increased pneumonia and myocardial infarction events.

Despite its limitations, STUDY 8 paved the way for the development of phase III trials addressing the combination of PARPi with different abilities to inhibit their target and ARSi with different mechanisms of action (abiraterone is an androgen biosynthesis inhibitor while enzalutamide is an AR antagonist). It is unclear whether these different mechanisms of action may affect a potential synergy between PARPi and ARSi. The three randomized phase III trials reported to date (MAGNITUD, PROPEL, and TALAPRO-2) have evaluated PARPi and ARSi combinations as first-line treatment for mCRPC and shared rPFS as the primary outcome, but otherwise had remarkably different designs including the prospective or retrospective HRR testing, the

stratifying factors, the percentage of patients with HRR and BRCA alterations or the prior use of ARSi (Table 3).

The PROpel trial[46] randomized 796 men to receive olaparib (300 mg bid) and abiraterone acetate (1000 mg/day) plus prednisone (10 mg/day) vs placebo and abiraterone as first-line treatment for mCPRC. Patients could have received docetaxel in the metastatic hormone-sensitive (mHSPC) stage but no prior ARSi was allowed. Participants were stratified by site of distant metastases and prior docetaxel at mHSPC. Tumor tissue and plasma samples were collected at study entry but HRR status was retrospectively analyzed. Aggregate data from tumor tissue and circulating DNA were used to classify patients as HRR mutant (HRRm, 28.4%), non-HRR mutant (non-HRRm, 69.3%), or unknown (2.3%), without significant differences noted between treatment arms. The study included 85 patients with *BRCA1/2* alterations. In the overall population, a benefit in rPFS was observed in patients receiving laparib and abiraterone (24.8 *versus* 16.6 months; HR 0.66, 95% CI 0.54–0.81), although the magnitude of the benefit varied by HRR status with *BRCA* altered patients benefiting the most (HR 0.23, 95% CI 0.12–0.43) followed by the broader HRRm subgroup (HR 0.50, 95% CI 0.34–0.73), and the Non-HRRm subgroup (HR 0.76; 95% CI 0.60–0.97). This benefit in rPFS only translated in more prolonged OS in patients with HRRm (HR 0.66, 95% CI 0.66–0.95) and particularly in those with *BRCA* alterations (HR 0.29; 95% CI 0.14–0.56). In the overall population, the 7.4 months improvement in OS (HR 0.81, 95% CI 0.67–1) was not statistically significant. The most frequent adverse events attributed to the combination included anemia (46%), fatigue/asthenia (37.2%), and nausea (28%). The most frequent grade $\geqslant$3 side effects in the experimental arm were anemia (15%), venous embolisms (6.8%), hypertension (3.5%), and fatigue (2.3%). Olaparib plus abiraterone is currently approved by EMA as first-line therapy for mCRPC patients regardless of HRR status while the FDA restricted the approval to *BRCA1* and *BRCA2* mCRPC patients.

The TALAPRO-2 trial[47] explored the use of enzalutamide (160 mg/day) in combination with talazoparib (0.5 mg/day) as first-line therapy for mCRPC. Prior treatment with docetaxel or abiraterone for mHSPC and HRR status were stratification factors. In cohort 1, the study enrolled 805 patients who were prospectively tested for HRR status on tumor tissue samples, detecting HRR alterations in 20.9% of participants. Median rPFS was significantly more prolonged in the combination arm (not reached *versus* 21.9 months, HR 0.63, 95% CI 0.51–0.78) in the overall population with a greater benefit in the HRR-deficient population (HR 0.46, 95% CI 0.3–0.7). Importantly, an exploratory analysis limited to patients without detectable HRR in tumor tissue suggests a benefit in rPFS from combining enzalutamide with talazoparib (HR 0.66, 95% CI 0.49–0.91), supporting preclinical reports of a synergy from the inhibition of the AR and HR pathways. The TALAPRO-2 study also included a second cohort of patients (cohort 2, $n = 230$) to expand the HRR deficient population to a total of 399, including 155 patients with *BRCA1/2* alterations,[59] and confirmed the rPFS benefit from the combination in this population (HR 0.44, 95% CI 0.32–0.60). Consistently with the PROPEL study, in TALAPRO-2 the greatest benefit was also observed in BRCA patients (HR 0.20, 95% CI 0.11–0.36). An exploratory analysis of cohort 2 suggests that as in monotherapy, the antitumor efficacy of PARPi combined with ARSi may depend on the HRR gene altered. The data presented at ASCO 2023[59] suggest limited benefit from the combination in patients with *ATM* alterations, but a potential advantage for patients with *CDK12* alterations that do not seem to respond to PARPi alone. Anemia was the most frequent side effect reported in the experimental arm (66%), followed by neutropenia (36%), fatigue (34%), thrombocytopenia (25%), decreased appetite (22%), and nausea (21%). Grade $\geqslant$3 hematological toxicities were frequent in the combination arm (anemia 46%, neutropenia 18%, and thrombocytopenia 7%).[47] Talazoparib plus enzalutamide is currently approved by the FDA as first-line therapy for HRR-deficient mCRPC patients.

MAGNITUDE[45,60] investigated the benefit of niraparib plus abiraterone as first-line treatment for mCRPC patients. An earlier phase Ib study recommended a dose reduction of niraparib to 200 mg/day (from 300 mg/day) when combined with abiraterone.[61] Eligible patients were prospectively screened for alterations in *ATM, BRCA1, BRCA2, BRP1, CDK12, CHEK2, FANCA, HDAC2*, and *PALB2* and included in cohort 1 if an alteration was present or in cohort 2 if no alteration was found. Patients could start abiraterone prior to randomization for up to

Table 3. Summary of phase III trials MGANITUDE, PROPEL, and TALAPRO-2.

		MAGNITUDE		**PROPEL**		**TALAPRO-2**	
AR signaling inhibitor		**Abiraterone (AA)**		**Abiraterone (AA)**		**Enzalutamide**	
PARP inhibitor		**Niraparib**		**Olaparib**		**Talazoparib**	
Study design	Inclusion criteria	1L mCRPC BPI-SF ⩽3 **⩽4 months AA for mCRPC** **HRR alt only**		1L mCRPC ECOG PFS 0-1 No prior AA in mCRPC ARSi allowed if stopped ⩾12 months prior All comers		1L mCRPC ECOG PFS 0-1 Docetaxel and AA for mHSCP allowed All comers	
	Molecular testing	**Prospective** Plasma: Resolution Biosciences Tissue: FoundationOne®CDx		**Retrospective** Tissue: FoundationOne®CDx Plasma:FoundationOne®Liquid CDx		**Prospective** Tissue: FoundationOne®CDx Plasma: FoundationOne®Liquid CDx	
	Genes analyzed	*ATM, BRCA1, BRCA2, BRP1, CDK12, CHEK2, FANCA, HDAC2, PALB2*		*ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L*		*ATM, ATR, BRCA1, BRCA2, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C*	
	Stratification factors	Prior docetaxel for mHSPC Prior ARSi for nmCRPC or mHSPC **Prior AA for 1L mCRPC** BRCA1/2 *versus* non-BRCA HRR		Site of metastases Prior taxane at mHSCP		**HRR status** Prior AA or docetaxel for mHSCP	
	Primary endpoint	**rPFS by central review in HRRm**		**rPFS by the investigator in all comers**		**rPFS by central reviewer in all comers**	
Population		*Experimental arm*	*Control arm*	*Experimental arm*	*Control arm*	*Experimental arm*	*Control arm*
	Patients	212	211	399	397	402	403
	HRRm	**100%**	**100%**	**28%**	**29%**	**21%**	**21%**
	Age, median (range), y	69 (45–199)	69 (43–88)	69 (43–91)	70 (46–88)	71 (41–90)	71 (36–91)
	PSA at study entry (ng/mL)	21.4 (0–4826.5)	17.4 (0.1–4400)	17.9 (6.09–67)	16.81 (6.26–53.3)	18.2 (0.1–2796)	16.2 (0.1–2285)
	ECOG						
	0	130 (61%)	146 (69%)	286 (72%)	272 (68%)	259 (64%)	271 (67%)
	1	82 (39%)	65 (31%)	112 (28%)	124 (31%)	143 (36%)	132 (33%)
	Site of metastases						
	Bone	183 (86.3%)	170 (80.6%)	349 (88%)	339 (85%)	349 (87%)	342 (85%)
	Visceral	**51 (24.1%)**	39 (18.5%)	55 (14%)	60 (15%)	57 (14%)	77 (19%)
	Prior docetaxel mHSPC	41 (19.3%)	44 (20.9%)	90 (23%)	89 (22%)	86 (21%	93 (23%)
	Prior ARPi for nmCRPC/mHSPC	8 (3.8%)	5 (2.4%)	1 (0.3%)	0	21 (5%)	25 (6%)
	Prior ARPi for L1 mCRPC	**50 (23.6%)**	**48 (22.7%)**	0	0	0	0

(Continued)

Table 3. (continued)

		MAGNITUDE		PROPEL		TALAPRO-2	
AR signaling inhibitor		**Abiraterone (AA)**		**Abiraterone (AA)**		**Enzalutamide**	
PARP inhibitor		**Niraparib**		**Olaparib**		**Talazoparib**	
Efficacy	rPFS all comers	_____		24.8 *versus* 16.6 months HR 0.66 (95% CI 0.54-0.81)		NR *versus* 21.9 months HR 0.63 (95% CI 0.5-0.78)	
	rPFS BRCA subgroup	19.5 *versus* 10.9 months HR 0.55 (95% CI 0.36-0.79)		NR *versus* 8.4 months HR 0.23 (95% CI 0.12-0.43)		NR *versus* 11 months HR 0.20 (95%CI 0.11-0.36)	
	rPFS HRRm subgroup	16.5 *versus* 13.7 months HR 0.73 (95% CI 0.56–0.96)		NR *versus* 13.9 months HR 0.50 (95% CI 0.34–0.73)		27.9 vs 16.4 months HR 0.46 (95% CI 0.3–0.7)	
	rPFS non-HRR/ unknown	_____		24.1 *versus* 19 months HR 0.76 (95% CI 0.60–0.97)		NR vs 22.5 months HR 0.70 (95% CI 0.54–0.89)	
	OS all comers	_____		42.1 *versus* 34.7 months HR 0.81 (95% CI 0.67–1.00)		36.4 *versus* NR months* HR 0.89 (95% CI0.69–1.14)	
	OS BRCA subgroup	HR 0.54 (95%CI 0.33–0.90)*		NR *versus 23* months HR 0.29 (95% CI 0.14–0.56)		HR 0.61 (95% CI 0.31–1.23)*	
	OS HRR subgroup	HR 0.70 (95%CI 0.49–0.99)*		NR-28.5 months HR 0.66 (95% CI 0.45–0.95)		NR *versus* 33.7 months* HR 0.69 (95% CI 0.46–1.03)	
	OS non-HRR/ unknown	_____		42.1 *versus* 38.9 months HR 0.89 (95% CI 0.7–1.14)		Not reported yet	
	Time to PSA progression	18.5 *versus* 9.3 months HR 0.57 (95% CI 0.43-0.76) $p < 0.001$		NR *versus* 12 months HR 0.55 95% CI 0.45-0.68)		26.7 *versus* 17.5 months HR 0.72 (95% CI 0.58-0.89) $p = 0.002$	
	Objective response rate (ORR)	60% *versus* 28% $p < 0.001$		58% *versus* 48% $p = 0.041$		62% *versus* 44% $p = 0.005$	
Safety	Frequent Adverse Events (Any grade – ⩾G3)	*Experimental arm*	*Control arm*	*Experimental arm*	*Control arm*	*Experimental arm*	*Control arm*
	Anemia	46–30%	20–8%	46–15%	16–3%	66–43%	16–4%
	Thrombocytopenia	21–7%	9–2%	<10%	<10%	25–5%	4–0.7%
	Neutropenia	14–6%	6–1%	<10%	<10%	36–17%	7–1%
	Nausea	24–0.5%	14–0	28–0.3%	13–0.3%	21–0.5%	13–0.7%
	Fatigue/asthenia	26–3%	17–4%	37–2.3%	28–2%	34–4%	29–2%
	Embolic/thrombotic events	<10%	<10%	9–8%	6–4%	3–2%	1–1%

*Immature overall survival data.
mCRPC, metastatic castration-resistant prostate cancer; NR, not reached; OS, overall survival; PSA, prostate-specific antigen; rPFS, radiologic progression-free survival.

4 months while testing was being performed. Run-in treatment with abiraterone and prior mHSPC treatment were the stratification factors. cohort 2 was closed after a pre-planned futility analysis suggested a lack of benefit from the combination in patients without HRR alterations. Cohort 1 finally included 423 patients, of which 190 (45%) had *BRCA1/2* alterations. The addition of niraparib to abiraterone resulted in more prolonged rPFS (16.5 *versus* 13.7 months; HR 0.76, 95% CI 0.6–0.97) with the greatest benefit also noted in the *BRCA1/2* subgroup (16.6 *versus* 10.9 months; HR 0.53, 95% CI 0.36–0.79). Anemia (46%), hypertension (31%), constipation

(31%), fatigue (26%), nausea (24%), thrombocytopenia (21.2%), and dyspnea (16%) were more frequent in the experimental arm. In this group, frequent grade ⩾3 toxicities included anemia (28.3%), hypertension (14.6%), and neutropenia (5.2%). Niraparib in combination with abiraterone has been approved by both, the FDA and EMA, as first-line therapy for mCRPC patients with *BRCA1/2* alterations.

An important conclusion from these three studies, PROPEL, TALAPRO-2, and MAGNITUDE is that a benefit hierarchy aligned with known biology can be established: BRCA2-deficient tumors >> all HRR-deficient tumors >> unselected patients >> HRR-proficient tumors.[62]

Future directions

PARPi are the first targeted therapies approved for the treatment of advanced prostate cancer but their use is being limited by the low testing rates.[63] Increased awareness and education are needed to encourage testing but also broader access to somatic genomic profiling to ensure that all patients with advanced disease have their tumors tested.

A major limitation to implementing PROPEL, TALAPRO-2, and MAGNITUDE in clinical practice is the differences between the population enrolled in those studies, mostly unexposed to prior ARSi, and the current and future mCRPC patients, the majority of whom have already received an ARSi for the treatment of mHSPC or non-metastatic castration-resistant prostate cancer (nmCRPC). The available evidence demonstrates that treatment with a second ARSi after disease progression to a prior one results in limited responses[64–66] and it has not been demonstrated that resistance to ARSi could be overcome by the addition of a PARPi. Furthermore, an exploratory analysis of the MAGNITUDE trial,[67] that allowed starting abiraterone before randomization reported decreased antitumor efficacy on patients who were on abiraterone ⩾2–4 months before starting niraparib, suggesting that the offset impact negatively the potential synergistic effect.

It will be important to understand the synergistic effect of ARSi and PARPi in early disease stages. AMPLITUDE[68] and TALAPRO-3[69] are, respectively, evaluating the combination of niraparib plus abiraterone and talazoparib plus enzalutamide in HRR-deficient mHSPC patients, previously unexposed to ARSi. This strategy is expected to extend the duration of hormone sensitivity and modify disease trajectory.

As mentioned earlier, patients will eventually become resistant to PARPi and there is currently no evidence for the management of patients with known BRCA1/2 alterations and/or HRR defects after disease progression to PARPi. Preclinical studies have shown that PARPi and platinum-resistant cancer models may be re-sensitized to PARPi when combined with other drugs that target molecular vulnerabilities, including cell cycle checkpoints[70] and replication stress.[71] Early-phase trials have shown a signal of activity with PARP inhibition re-challenge in combination with ATR or Wee1 inhibition in various tumor types. Other potent inhibitors that target different key nodes along the DNA damage repair cascade are also in clinical development, including *CHK1/2, DNA-PK, ATM*, and *POLθ* inhibitors,[72] which may represent other potential combination partners for PARPi.

Finally, a new generation of selective PARP1 inhibitors without activity upon PARP2, expected to retain anticancer efficacy with decreased toxicity, is being developed.[73]

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Maria Teresa Bourlon: Conceptualization; Methodology; Supervision; Writing – original draft; Writing – review & editing.

Paola Valdez: Conceptualization; Investigation; Writing – original draft; Writing – review & editing.

Elena Castro: Conceptualization; Data curation; Investigation; Methodology; Project administration; Supervision; Validation; Writing – original draft; Writing – review & editing.

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