PARP inhibitors in prostate cancers, is it time for combinations?

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Review

PARP inhibitors in prostate cancers, is it time for combinations?

Diego Teyssonneau, Charles Dariane, Eric Barret, Jean-Baptiste Beauval, Laurent Brureau, Gaëlle Fiard, Gaëlle Fromont, Gilles Créhange, Mathieu Gauthé, Alain Ruffion, Raphaële Renard-Penna, Romain Mathieu, Paul Sargos, Morgan Rouprêt, Guillaume Ploussard and Guilhem Roubaud, on behalf of the CC-AFU, Cancerology Committee of the Association Française d'Urologie

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***Abstract*:** Despite several improvements in outcomes, metastatic prostate cancer remains deadly. Alterations in the homologous recombination repair (HRR) pathway are associated with more aggressive disease. Olaparib and rucaparib, two poly-ADP-ribose polymerase (PARP) inhibitors, have received approval from the authorities of several countries for their anti-tumoral effects in patients with metastatic castration-resistant prostate cancers harboring HRR gene alterations, in particular *BRCA2*. More recently, it has been hypothesized that new hormonal therapies (NHTs) and PARP inhibitors (PARPi) could have synergistic actions and act independently of HRR deficiency. This review proposes to discuss the advantages and disadvantages of PARPi used as monotherapy or in combination with NHTs and whether there is a need for molecular selection.

Keywords: DNA repair, homologous recombination repair, metastatic prostate cancers, PARP inhibitors

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Background

Despite several improvements in outcomes, metastatic castration-resistant prostate cancer (mCRPC) remains the fifth leading cause of cancer death in men worldwide.[1] While the androgen receptor (AR) pathway plays a central role, recent studies have highlighted the significance of DNA repair pathways in tumor growth and progression, particularly the homologous recombination repair (HRR) system.[2,3] Furthermore, it seems that germline and somatic HRR-deficient (HRD) prostate cancers are more aggressive and less responsive to taxane-based chemotherapies compared to others.[4–7] Approximately one in four patients exhibit HRD due to germline or somatic alterations in HRR genes, mainly *BRCA2*, *ATM*, *CDK12*, and *CHEK2*.[3]

Proteins involved in the HRR system are crucial for repairing double-strand breaks (DSBs), while poly-ADP-ribose polymerases (PARPs) are primarily involved in repairing single-strand breaks (SSBs).[8–13] PARP inhibitors (PARPi) prevent PARP action through catalytic or trapping inhibition, inducing SSB accumulation that will eventually be converted into DSB during replication. HRD cells are unable to repair DSBs leading to apoptosis.[14] Based on this concept of synthetic lethality, several studies have assessed the efficacy of PARPi in HRD mCRPC, demonstrating positive outcomes in terms of survival.[15,16]

On the other hand, preclinical studies have indicated that the AR pathway promotes transcriptional programs of genes involved in DNA repair and that androgen deprivation therapies (ADTs) and new hormonal therapies (NHTs) may induce a BRCAness state independent of the genomic HRR status.[17–19] Based on this rationale, three phase III trials evaluating the combination of PARPi and NHT have shown promising results (Table 1).[20–22]

Table 1. Summary of phase III trials using PARPis for metastatic prostate cancers.

Type	Name	Study population	HRR status	Previous NHT (%)	Stratification of HRR status	Standard arm	Intervention	Primary endpoint	Main results
Monotherapy	PROfound[15,23] (olaparib)	mCRPC ⩾ 1 NHT	-BRCA/ATM cohort -Other HRD cohort	100	No	NHT	Open label Cross over allowed	rPFS BRCA/ ATM cohort (BICR)	-↑ rPFS[23] and OS[15] BRCA/ATM $p < 0.001$ and $p = 0.02$
	TRITON-3[16] (rucaparib)		BRCA/ATM		Yes (BRCA1 *versus* BRCA2 *versus* ATM)	Docetaxel or NHT		rPFS (BICR)	-↑ rPFS[16] study population $p < 0.001$ -↑ rPFS BRCA1/2[16] $p < 0.001$ - rPFS ATM[16] p not reported
Combination with NHT	PROpel[20,24] (olaparib/AAP)	L1 mCRPC	All comers	<1	No	NHT	Double-blinded No cross over	rPFS (IA)	- ↑ rPFS[20] $p < 0.001$ - OS[24] $p = 0.054$
	MAGNITUDE[21,25] (niraparib/AAP)		-HRD cohort -HRP cohort (stopped for futility)	3	Yes (BRCA1/2 *versus* other)			- rPFS BRCA1/2 (BICR) - rPFS HRD cohort (BICR)	-↑ rPFS[21] and OS[25] BRCA1/2 $p < 0.001$ and $p = 0.024$ -↑ rPFS HRD cohort[21] $p = 0.028$ - rPFS HRP cohort[21] $p = 0.66$
	TALAPRO-2 all comers[22] (talazoparib/ enzalutamide)		All comers	6	Yes (HRP *versus* HRD)			rPFS (BICR)	-↑ rPFS all comers[22] $p < 0.001$ -↑ rPFS HRD[22] $p = 0.0006$ -↑ rPFS HRP[22] $p = 0.0035$
	TALAPRO-2 HRD[26] (talazoparib/ enzalutamide)		HRD	8	Yes (BRCA1/2 *versus* other HRD)			rPFS (BICR)	-↑ rPFS[26] $p < 0.0001$ -↑ rPFS BRCA1/2[26] $p < 0.0001$ - rPFS other HRD[26] $p = 0.06$

AAP, abiraterone acetate and prednisone; BICR, blinded independent central review; HRD, HRR deficient; HRP, HRR proficient; HRR, homologous recombination repair; IA, investigator-assessed; mCRPC, metastatic castration-resistant prostate cancer; NHT, new hormonal therapy; PARPi, poly-ADP-ribose polymerase; rPFS, radiographic progression-free survival.

This article aims to discuss the advantages and disadvantages of PARPi used as monotherapy or in combination with NHT.

PARPi used as a monotherapy

The PROfound trial was the first to investigate the efficacy of olaparib in men with mCRPC featuring somatic or germline mono or bi-allelic HRR alterations previously treated with at least one NHT.[15,23] They were randomly assigned to receive the physician's choice of NHT or olaparib. The trial met its primary endpoint of median rPFS in cohort A (*BRCA1/2* or *ATM* alterations; 7.4 *versus* 3.6 months, HR: 0.34, $p < 0.001$).[23] Despite 84% of the patients in the control group crossing over upon progression, cohort A patients exhibited significantly higher overall survival (OS).[15] No difference between the physician's choice of NHT and olaparib was observed in cohort B (other HRR alterations). In addition, the olaparib group in cohort A demonstrated a better preserved quality of life.[27] The main limitation of this study lies in its weak control arm, the NHT; the use of docetaxel might have been more appropriate.

Rucaparib was evaluated in the TRITON-3 trial, including mCRPC patients harboring *ATM* or *BRCA1/2* alterations, previously treated with at least one NHT.[16] Patients were randomly assigned to receive either rucaparib or physician's choice treatment (docetaxel or NHT). The study met its primary endpoint, with a longer rPFS in the experimental group for both the overall and BRCA populations (10.2 *versus* 6.4 months, $p = 0.0003$ and 11.2 *versus* 6.4 months, $p < 0.0001$, respectively) and a good safety profile. A *post hoc* analysis confirmed the benefit of rucaparib compared to docetaxel which served as a stronger control arm than in the PROfound trial.[16]

Neither of these two trials showed improvements in the *ATM* population.[16,28] Furthermore, in an exploratory gene-by-gene analysis of PROfound, no benefit in terms of rPFS or PSA decline was observed in the analysis of *CDK12* and *CHEK2* genes, potentially due to a lack of efficacy or limited sample size.[28] Data are currently unavailable for other HRR genes.

These two studies demonstrated the benefits of using PARPi compared to NHT or even docetaxel for pre-treated mCRPC patients with *BRCA1/2* alterations. More data are required for other HRR genes. Some questions remain unanswered, such as the impact of germinal or somatic status as well as zygosity, the optimal test to be used (liquid *versus* solid biopsies, broad *versus* targeted NGS), and the cost of their use.

To enhance the efficacy of PARPi, overcome primary resistance, and facilitate their use, combinations of PARPi with NHT were evaluated in three phase III studies. These studies are described in the next paragraph.

PARPi used in combination

It has been shown that the AR pathway promotes transcriptional programs of DNA repair genes and that NHT downregulates their transcription. More recently, two studies have shown that the use of ADT or enzalutamide could result in a BRCAness state, leading to PARPi sensitivity.[17–19] Moreover, *RB1* and *BRCA2* are closely localized in chromosome 13q, and codeletions of *BRCA2* and *RB1* can emerge under selection pressure, being associated with aggressiveness and a poor response to NHT.[29,30] Therefore, it is hypothesized that PARPi could suppress early clones resistant to NHT.[31]

Based on this rationale and the phase II STUDY-08,[32] PROpel enrolled patients with first-line mCRPC, regardless of their HRR status.[20] Patients were randomly assigned to receive abiraterone in combination with either olaparib or placebo. Approximately 28% of the patients had an HRR alteration, and 10% had a BRCA alteration. The study met its primary endpoint as rPFS was longer with the combination compared to placebo in the overall population (24.8 *versus* 16.6 months, $p < 0.001$). This improvement seems to be found in the HRD population and to a lesser extent in the HRR-proficient (HRP) population.[20] Final OS analysis showed a trend toward improvement in the all-comers population ($p = 0.054$, 48% maturity). However, subgroup analyses suggested that this efficacy was found only in the *BRCA* and HRD cohorts, not in the non-*BRCA* and HRP cohorts.[24] As expected, more cases of anemia, fatigue, and nausea were observed in the experimental group. However, no additional cases of cardiac failure were reported, compared to the STUDY-08.[32]

The MAGNITUDE trial enrolled patients with mCRPC in first-line treatment.[21] Patients were divided into two pre-specified cohorts: HRD and

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HRP. Patients of each cohort were randomized to receive abiraterone in combination with either niraparib or placebo. The study met its primary endpoint as rPFS was significantly improved in the combination arm compared to the experimental arm, in both BRCA and HRD populations (19.5 *versus* 10.9 months, $p < 0.001$ and 16.7 *versus* 13.7 months, $p = 0.028$, respectively).[33] No difference was observed in the subgroup of patients with HRR alterations other than *BRCA1/2*. OS was improved in the combination arm in the BRCA population (30.4 *versus* 28.6 months, nominal $p = 0.024$ adjusted on multivariate analysis).[25] The preplanned futility analysis in the HRP group (233 patients) did not show any benefit of adding niraparib to abiraterone, leading to the close of the study cohort.

Finally, TALAPRO-2 is the latest such trial studying the association of enzalutamide with either talazoparib or placebo, as the first line for mCRPC.[22] Patients were enrolled in two cohorts: the all-comers (cohort 1, 805 patients) and the HRD (cohort 2, 399 patients). The study was positive with a longer rPFS in the combination group of the all-comers population [not-reached (NR) and 21.9 months, $p < 0.001$]. Subgroup analyses showed an improvement in the HRD (169 patients) and the non-HRD groups (636 patients), HR = 0.45 (0.29–0.69, $p = 0.0002$), and HR = 0.66 (0.49–0.91, $p = 0.009$), respectively. The toxicity profile was comparable to previous studies but with more severe anemia and neutropenia. Results from cohort 2 (HRD only) were recently reported, confirming a longer rPFS in the combination group.[26] More interestingly, results from patients with HRD other than BRCA were analyzed (244 patients); however, despite a trend of improvement, the results were not statistically significant ($p = 0.10$).

These three combination trials met their primary endpoints: rPFS improvement in the all-comers population for PROpel and TALAPRO-2, and the HRD population for MAGNITUDE. Moreover, PROpel and TALAPRO-2 suggested a benefit for rPFS in the HRP population, using subgroup analyses, whereas this was not shown in the MAGNITUDE trial designed with a separate cohort.

Discussion

The PROfound and TRITON-3 trials demonstrated convincing results for the use of PARPi as monotherapy in patients with mCRPC and *BRCA*1/2 alterations after NHT. However, the improvement is debatable for *ATM* and other HRR genes, and PARPi used as monotherapy is inefficient in HRP patients.[15,16,34] To overcome resistance and enhance efficacy, the synergistic action of PARPi and NHT was evaluated in PROpel, MAGNITUDE, and TALAPRO-2 for mCRPC patients as first-line setting (Figure 1).

BRCA1/2-*altered patients*

The efficacy of PARPi, whether used as monotherapy or in combination with NHT, for *BRCA2*-altered mCRPC, is undeniable. However, it should be stressed that most of studies do not differentiate between *BRCA1* and *BRCA2* alterations, and since *BRCA1* alterations are less common, trials are underpowered to assess efficacy for these later alterations.[2,3] Moreover, the question of the optimal sequence is largely unanswered. It is still unclear whether PARPi should be used in combination, even earlier than in the mCRPC setting. Furthermore, it is unclear whether it may increase toxicities without actually providing any survival benefit and whether it is better to administer NHT and PARPi simultaneously or use them sequentially.

PROfound and TRITON-3 taught us that PARPi as monotherapy is more efficient than NHT, and, most importantly, more efficient than docetaxel in the mCRPC setting after at least one prior exposure to NHT.[15,16] Moreover, a *post hoc* analysis suggested a broader effect of olaparib when given before rather than after docetaxel.[35] It could suggest that the earlier PARPi are given, the better the outcomes.

Regarding combinations, only a small proportion of the patients (0.8%, 2%, and 34%) have received PARPi as subsequent therapies in the control arm of PROpel, TALAPRO-2 all comers, and MAGNITUDE, respectively. Therefore, given the results of the PROfound and TRITON-3 trials, there is a bias and they cannot adequately address the question of the optimal sequence, even if an OS improvement is observed.[29,25] The phase II BRCAAway trial randomized 60 patients with mCRPC and *BRCA1/2* or *ATM* alterations in three arms: the first received abiraterone, the second Olaparib, and the third a combination of both.[36] Updated data were recently presented, and it was observed that patients in the combination group had greater Prostate-specific antigen (PSA) responses and longer PFS compared to the two other arms suggesting a synergistic or additive

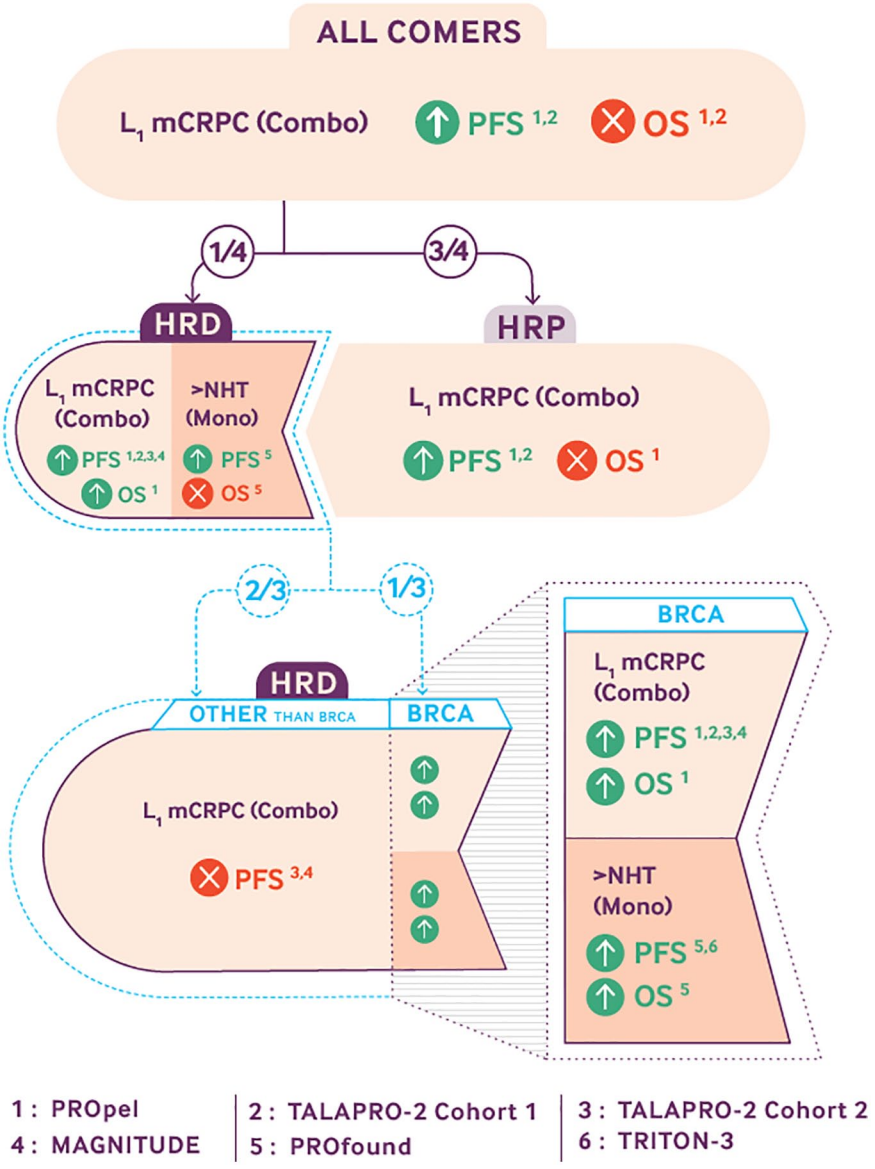

Figure 1. Main results provided by the five phase III trials studying PARPis in metastatic prostate cancers. PROpel,[20,24] TALAPRO-2 cohort 1,[22] TALAPRO-2 cohort 2,[26] MAGNITUDE,[21,25] PROfound,[15,23] and TRITON-3.[16]

action between the two drugs. However, no OS data were reported.[37] Thus, although there is a tendency toward the superiority of the combination, without OS data, the question of the best sequence currently remains unanswered. Ongoing trials investigating such combinations in castration-sensitive settings will provide additional information (NCT04821622 and NCT04497844).

HRR alterations other than BRCA1/2

PARPi monotherapy does not appear to be effective for *ATM* or *CDK12* alterations, and data are lacking for other HRR genes to decipher their predictive implications.[38] Can the combination of PARPi and NHT enhance efficacy and overcome primary resistance?

PROpel is currently the only trial with data on OS in the all HRD population, and it demonstrated an undeniable benefit (HR: 0.50, 95% CI: 0.34–0.73).[24] However, it should be noted that BRCA-altered patients represented approximately 30% of HRD patients, and the OS benefit was even more pronounced in this subgroup (HR: 0.23, 95% CI: 0.12–0.43). Therefore, the question can

be raised of whether the majority of the observed benefit in the HRD group should be attributed to *BRCA1/2*-altered patients. Investigators in both MAGNITUDE and TALAPRO-2 separated BRCA patients from other HRD patients. Unfortunately, with relatively small-sized populations (200 and 244, respectively), they failed to show an improvement. Nevertheless, trends toward improvement were observed when clustering some genes such as those implicated in the HRR-Fanconi pathway (*BRIP1*, *FANCA*, and *PALB2*), or *CDK12* cluster.[26,39] Therefore, the combination could be of interest for certain HRR alterations, but more data are needed to identify the specific genes of interest.

HRR-proficient patients

The PROpel and TALAPRO-2 trials showed a modest benefit in rPFS for the HRR-proficient population through subgroup analyses, whereas this was not observed in the MAGNITUDE trial which used distinct cohorts. Although the data regarding the non-HRD population in TALAPRO-2 came from a secondary endpoint and a subgroup analysis, they were consistent as patients were stratified.[22] Results from PROpel were less robust as patients were not stratified on their HRR status. Unfortunately, enrollment in the HRP cohort of the MAGNITUDE study was halted after the preplanned futility analysis. These contradictory outcomes are difficult to explain and merit attention considering that the design of the MAGNITUDE trial was the most robust. Moreover, the patient populations were quite similar across the trials. The early discontinuation of enrollment in the HRP cohort of MAGNITUDE may have occurred due to the use of a composite endpoint of time to PSA progression and/or rPFS, rather than solely rPFS. A modest benefit of the combination cannot be precluded with the limited size of the cohort.

Moreover, a recent quantitative meta-analysis of these three trials suggested a rPFS improvement of the combination. However, quantitative meta-analyses involve biases and are less robust than individual patient data meta-analyses.[40] Therefore, given these contradictory outcomes, the combination of PARPi and NHT could be an interesting option for HRP patients and requires monitoring, but more robust data are needed, especially regarding OS and long-term toxicity.

Conclusion

PARPi alone are well tolerated and highly effective for patients with *BRCA1/2* alterations; these patients should all receive PARPi at some point in their medical history. However, PARPi efficacy is unclear for other HRR genes, and they should not be used alone for HRP patients. The combination with NHT could overcome resistance and, based on PROpel, MAGNITUDE, and TALAPRO-2 trials, three patient profiles can be delineated:

-For *BRCA1/2*-altered patients, although an OS improvement was reported in PROpel and MAGNITUDE trials, a large portion of patients did not receive PARPi as a subsequent therapy in their control arms. Therefore, we cannot confirm that the combination is superior to the sequence for the moment.
-For HRD patients with alterations other than *BRCA1/2*, MAGNITUDE, and TALAPRO-2 showed an improvement trend that was not statistically significant, indicating the need for more data. PROpel did not specifically analyze these cases.
-For HRP patients, subgroup analyses suggest that the combination may provide a modest rPFS benefit in two out of three studies. However, negative results from MAGNITUDE raise questions and rPFS is not a validated surrogate marker of OS for first-line mCRPC in the setting of PARPi therapy.

Overall, the results of these studies raise questions and fuel debates.[41,42] Is there a subset of patients in the HRP group harboring another alteration than a canonical HRR mutation, conferring excellent response? Were the HRR alterations well tested, and were there some HRD patients in HRP cohorts? Indeed, approximately one-quarter of the PROpel patients were only evaluated using circulating tumor DNA in the absence of adequate tumor tissue. Are these modest improvements worth the potential increased toxicities?

Furthermore, we must consider the cost-effectiveness of such combinations in an all-comers strategy. Moreover, only a small number of patients in the combination trials received previous NHT, whereas nowadays every patient's treatment should be intensified with NHT in the castrate-sensitive state. Therefore, without data on the efficacy of the combination of PARPi and

NHT in a pre-exposed setting, there is a risk of cross-resistances changing NHT instead of chemotherapy as first-line mCRPC treatment. Faced with all these questions, the majority of experts from the Advanced Prostate Cancer Consensus Conference do not recommend the use of the combination for patients with an HRR alteration other than BRCA or patients without any HRR alteration. A consensus could not be reached regarding the use of the combination in patients with a BRCA alteration.[42]

Finally, it is important to emphasize that regardless of future results, it will always be important to undergo a *BRCA1/2* screening so both family history and more aggressive cancers are not overlooked.[4–6]

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Author contributions
Diego Teyssonneau: Conceptualization; Writing – review & editing.

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Jean-Baptiste Beauval: Validation.

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