THEMATIC REVIEW

# PARP inhibitors in advanced prostate cancer: when to use them?

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## Abstract

Poly (ADP-ribose) polymerase (PARP) inhibitors have antitumor activity in advanced prostate cancer associated with loss of homologous recombination repair (HRR) function. About 20% of all patients with advanced prostate cancer present germline or tumor mutations in HRR-related genes, the most common being *BRCA2*, mutated in approximately 10% of all advanced prostate cancers. Challenges related to sample availability, tumor heterogeneity and access to NGS technology need to be addressed for a successful implementation of genomic stratification in routine clinical practice. The recent regulatory approvals of PARP inhibitors olaparib and rucaparib represent the first molecular biomarker-guided drugs for men with prostate cancer. While these findings represent a significant advance in the field of precision medicine and prostate cancer, there are still many unsolved questions on the optimal use of PARP inhibitors in this disease. Several clinical trials have shown that different mutations in various genes are associated with distinct magnitudes of sensitivity to PARP inhibitors, with *BRCA2* mutations associating with more frequent and durable responses, questioning the benefit for subset of patients with mutations in other HRR-associated genes. In this review, we scrutinize the clinical development of different PARP inhibitors for the treatment of advanced prostate cancer, and we discuss how the study of additional biomarkers and the design of rational drug combinations can maximize patient benefit from this drug class.

**Key Words**

- prostate cancer
- genomics
- liquid biopsy
- CTC
- cfDNA
- extracellular vesicles
- precision medicine

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## Introduction

Prostate cancer represents the most common cancer among men in the Western world. It is expected that 1 in 8 men in Europe and North America will be diagnosed with prostate cancer at some point during their lives; incidence increases with age. Importantly, while most prostate cancers are diagnosed as localized disease and can be treated successfully, metastatic prostate cancer is an invariably fatal condition, being the third cause of cancer-related death among men in Europe, and the second in the United States (Culp *et al.* 2020, Randi *et al.* 2020, Siegel *et al.* 2021).

Androgen receptor (AR) signaling is the key driver of prostate cancer, as reviewed elsewhere in this special issue, and blocking gonadal testosterone with luteinizing

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hormone-releasing hormone (LHRH) agonists or antagonist, an approach commonly referred to as chemical castration or androgen deprivation therapy (ADT), remains the mainstay of systemic treatment (Sharifi *et al.* 2010, Lepor & Shore 2012). In recent years, we have seen a number of new drugs added to the therapeutic armamentarium for this disease: chemotherapy with taxanes, as well as novel hormonal agents further targeting the androgen receptor signaling axis (such as abiraterone acetate, enzalutamide, darolutamide or apalutamide) have improved prognosis of patients with metastatic prostate cancer, either when used upfront at initial diagnosis (Sweeney *et al.* 2015, Vale *et al.* 2016, James *et al.* 2017, Rydzewska *et al.* 2017, Kyriakopoulos *et al.* 2018, Armstrong *et al.* 2019, Chi *et al.* 2019, Davis *et al.* 2019) or after the development of ADT-resistance (metastatic castration-resistant prostate cancer, mCRPC) (de Bono *et al.* 2010, 2011, Saad & Hotte 2010, Scher *et al.* 2012, Ryan *et al.* 2015, Beer *et al.* 2017). Additionally, Radium-223, an alfa-emitter radio-particle with the selective property to bind bone lesions, prolonged median overall survival (OS) and enhanced quality of life compared with placebo in the ALSYMPCA trial (Parker *et al.* 2013).

Despite these advances, metastatic prostate cancer remains a deadly disease, and further novel therapeutic approaches are needed. An improved understanding of the genomic landscape of lethal prostate cancer allows for reclassifying this disease based on predictive biomarkers for specific drugs, aiming for accelerating the development of precision medicine strategies for advanced prostate cancer. The recent approvals of poly (ADP-ribose) polymerase (PARP) inhibitors olaparib and rucaparib constitute a first-ever landmark in the management of prostate cancer (Abida *et al.* 2020, de Bono *et al.* 2020*a*, Mateo *et al.* 2020*a*). In contrast to many other tumor types, no drugs had ever been approved until now on the basis of a predictive genomic biomarker in the field of prostate cancer. However, many questions need yet to be addressed to optimize the use of PARP inhibitors in prostate cancer, including which are the optimal predictive biomarkers, what would be the more efficient framework to routinely test men with advanced prostate cancer for these biomarkers, and when along the disease natural history would the use of PARPi result in major benefit for patients.

Herein, we review the current evidence for using PARP inhibitors in molecularly-defined subsets of advanced prostate cancer, discuss some of the currently open questions about which patients should receive these drugs and identify key gaps in knowledge that research in the field should try to address in order to maximize the potential of PARP inhibitors for patients suffering from advanced prostate cancer.

## DNA repair gene alterations in prostate cancer

While AR-dependent transcriptional activity is the main driver of prostate cancer progression, genomic instability is also a major feature of prostate cancer. Prostate cancer is enriched for structural variants, including gene rearrangements, indels and copy number alterations rather than point mutations. In part, this genomic instability seems to be related to AR signaling and chronic inflammation leading to increased DNA damage (Goodwin *et al.* 2013, Polkinghorn *et al.* 2013). Moreover, alterations inactivating key double-strand break repair genes are common in prostate cancer, and their prevalence increases in advanced disease states. These mutations would lead to a relative impairment of error-free homologous recombination-mediated repair, so the cell will preferentially rely on error-prone DSB repair systems, favoring genomic instability and replicative stress. These mutations have been found in key genes of the HRR pathway, mainly *BRCA2*, but also *BRCA1, FANCA, RAD51* or *PALB2*; and in genes indirectly involved in HRR, that is, *ATM*, *CHEK2* or *CDK12* (Robinson *et al.* 2015).

In the localized or locoregional disease setting, the prevalence of HRR-associated gene mutations is probably below 10%, although figures vary significantly among studies. In the TCGA consortium study (Abeshouse *et al.* 2015), including whole-exome sequencing of 333 tumor samples, the prevalence of *BRCA1* and *BRCA2* mutations was 1 and 3%, respectively, whereas the prevalence of *ATM* mutations was 4% and, for *CDK12* mutations, it was 2%.

On the other side of the clinical spectrum, the SU2C-PCF Prostate Cancer Dream Team consortium reported whole-exome sequencing (WES) for over 400 metastatic biopsies from patients with advanced stages of prostate cancer (Robinson *et al.* 2015, Abida *et al.* 2019). The prevalence of *BRCA2* alterations in this late-stage population was 11%, 2% for *BRCA1*, 7% for *ATM* and 7% for *CDK12*; together, around 20–25% of patients with metastatic prostate cancer presented deleterious alterations in HRR-associated genes. This large series of metastatic cases undergoing WES analysis permitted the identification of less common, but potentially clinically relevant mutations in other HRR genes such as *PALB2*, *RAD50*, *RAD51* or *BRIP1*; all of these alterations have a prevalence of <1–2% each in metastatic prostate cancer. It is possible that the true prevalence of HRR alterations in advanced prostate cancer is even higher, as other mechanisms of gene inactivation, such as certain structural rearrangements or epigenetic silencing, could be missed in WES analysis. For

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example, *BRCA1* methylation is a common mechanism of gene silencing in ovarian cancer (Aref-Eshghi *et al.* 2020), but the prevalence in prostate cancer is unknown.

## Clinical testing for HRR mutations in prostate cancer

Multiple studies have now confirmed the high prevalnece of HRR-associated gene mutations in advanced prostate cancer (Abida *et al.* 2017, Chung *et al.* 2019, Stopsack *et al.* 2020). This enrichment in late-stage disease has led to some controversy with regards to the use of archival, primary prostate tumor biopsies for genomic profiling once patients have developed mCRPC. As part of the screening process for the randomized PROFOUND trial of olaparib, over 4000 patients underwent next-generation sequencing (NGS) targeted profiling; the overall rate of HRR-associated genes mutations was 27%, with no differences observed based on the use of a primary vs metastatic sample for NGS testing (de Bono *et al.* 2020*a*). Similarly, in a study pursuing targeted NGS from 470 primary tumors of patients who all later developed mCRPC, the prevalence of these mutations was similar to what has been reported for metastatic biopsy cohorts (Mateo *et al.* 2020*b*). Moreover, a recent study comparing primary tumor biopsies and cfDNA samples acquired later at the time of mCRPC also confirmed that *BRCA2, ATM* and *CDK12* defects are already present in the primary tumors of these patients (Warner *et al.* 2021). This is different to the study of alterations in *AR* or tumor suppressors such as *TP53*, *RB1* or *PTEN*, which seem to evolve as a result of hormonal therapy-induced selective pressure.

Two potential drawbacks of using primary archival tumor biopsies for mCRPC stratification based on HRR mutations are (1) the multifocal nature of prostate cancer, which may result in the core biopsy analyzed not representing the metastatic disease clone (Boutros *et al.* 2015), and (2) the small size of prostate primary tumor biopsies and progressive degradation of DNA after years in paraffin, making up to 20–30% of core biopsies unsuitable for NGS testing using commercial platforms (de Bono *et al.* 2020*a*).

Some of these mutations arise in germline DNA. Germline *BRCA2* mutations increase the risk of developing prostate cancer by eight-fold by the age of 65 years (Kote-Jarai *et al.* 2011). In the localized and locoregional prostate cancer setting, germline *BRCA1/2* alterations have been associated with poor outcome, including disease progression among patients undergoing active surveillance (Carter *et al.* 2019) or higher risk of recurrence and death among patients undergoing salvage therapy (Castro *et al.* 2013, 2015). While the data in the advanced disease setting is less robust, it also seems germline *BRCA2* mutation carriers have a more aggressive disease course (Castro *et al.* 2019). The prevalence of germline mutations varies among countries and ethnic groups, but all studies concur in the enrichment among men with metastatic prostate cancer, compared to patients with localized prostate cancer; in a landscape studies including seven academic institutions from US and UK, 82/692 (12%) men with metastatic prostate cancer carried germline mutations in DNA repair genes (Pritchard *et al.* 2016). Germline *BRCA2* mutations were the commonest, with a prevalence of 5%. The NCCN guidelines now recommend pursuing germline sequencing for all men with node-positive or metastatic prostate cancer, as well as to some subgroups of patients with localized disease and either high-risk features or a strong family history of cancer (Freedman-Cass *et al.* 2021).

## PARP inhibitors: from bench to bedside

Poly (ADP-ribose) polymerases (PARP), a family of enzymes sharing a catalytical domain whose main function is to add poly-ADP-ribose (PAR) chains to other proteins as signaling transmitter and/or to regulate transcription. PARP1, predominantly, and PARP2, are critical to DNA single-strand break (ssDNA) repair. They detect ssDNA breaks, bind to them and synthesize PAR using $NAD^+$, initiating the call for DNA repair mediators and effectors, which then will require PARP1/2 to be removed from the site of damage for the ssDNA repair process to properly ensue. PARP inhibitors are drugs that compete with $NAD^+$ to bind to the enzyme, and therefore prevent proper activation of the ssDNA break repair cascade.

Unrepaired ssDNA breaks will progress to double-strand DNA (dsDNA) breaks. However, cells have specific pathways to repair toxic dsDNA breaks, including the error-prone non-homologous end joining (NEHJ) and microhomology-mediated end joining (MMEJ) pathways and the preferred, error-free, homologous recombination repair (HRR) pathway.

PARP inhibition will result in the progression of unrepaired ssDNA breaks to dsDNA breaks; in an HRR deficient context, such as those tumors with *BRCA1/2* mutations, errors will accumulate and drive the tumor cell toward catastrophe. Moreover, a direct cytotoxic effect of PARP inhibitors results from the 'trapping' effect: PARP inhibitors will trap PARP proteins to the ssDNA damage

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sites, not allowing their release (which is necessary for the mediator proteins to initiate repair). The trapped PARP proteins will cause replication fork stalling, increasing replication stress to a non-tolerable level for the tumor cell, thus contributing to tumor cell death. Non-tumoral, HRR proficient cells, however, will spare the effect of PARP inhibitors, as accumulated dsDNA breaks will be repaired by HRR. This interaction between PARP inhibition and HRR loss of function represents a prime example of how the concept of synthetic lethality can be applied to anticancer drug development.

In 2005, two back-to-back papers demonstrated how PARPi silencing by siRNA or pharmacological blockade resulted in selective killing of BRCA1/2 deficient tumor models but not *BRCA1/2* wild-type (WT) cells (Bryant *et al.* 2005, Farmer *et al.* 2005). Further studies in cancer preclinical models suggest that loss of other proteins involved in HRR can also sensitize to PARP inhibition, although the magnitude of sensitizing may vary depending on the exact protein that is lost (McCabe *et al.* 2006, Murai *et al.* 2012). These data triggered the clinical development of PARP inhibitors, initially focused in cancer patients with germline mutations in *BRCA1/2* genes, as shown in the proof-of-concept first-in-man trial of olaparib (Fong *et al.* 2009, Audeh *et al.* 2010).

Several PARP inhibitors are approved for the treatment of ovarian cancer; these include patients with *BRCA1/2* mutations but also as maintenance therapy for patients responding to platinum-based chemotherapy (Mirza *et al.* 2016, 2020, Coleman *et al.* 2017, Pujade-Lauraine *et al.* 2017, Moore *et al.* 2018). In breast and pancreatic cancer, the registration trials focused in patients with germline *BRCA1/2* mutations (Robson *et al.* 2017, Golan *et al.* 2019).

## Clinical evidence for PARP inhibitors in prostate cancer

Few patients with advance prostate cancers carrying germline *BRCA1/2* mutations were included in the phase I studies of the different compounds, but preliminary evidence of the antitumor activity of PARPi in prostate cancer was observed (Fong *et al.* 2009). Then, the phase I trial of niraparib explored the antitumor activity in a cohort of 'sporadic' prostate cancers (Sandhu *et al.* 2013), observing several cases with durable disease stabilizations and drops in circulating tumor cell counts.

The TOPARP trial provided proof-of-concept data for the development of PARP inhibitors in advanced prostate cancer (Mateo *et al.* 2015, 2020*a*). The first part of this adaptive phase II trial evaluated the response to olaparib among 49 men with mCRPC, defining response as either a radiological response according to RECIST, a PSA response >50% and/or a confirmed circulating tumor cells (CTC) count conversion from high to low counts. Overall, 33% (16/49 patients) achieved at least one of the criteria to be classified as a responder, including 11 patients with PSA responses and 6 confirmed radiological responses (among 32 patients with RECIST-evaluable disease). One of the key objectives of the study was to identify a biomarker suite that would identify those patients benefiting from olaparib treatment. Fresh metastatic biopsies were acquired from all trial participants prior to starting olaparib treatment, and molecular studies were retrospectively correlated with clinical outcome. Loss of PTEN expression or the presence of *ERG* rearrangements were not found to associate with responses; contrarily, the presence of germline or somatic mutations in DNA repair genes (including *BRCA1, BRCA2, ATM* or *PALB2*) was enriched among responding patients. Indeed, all seven patients with *BRCA2* alterations responded, but interestingly, tumor responses in the form of CTC count conversions and PSA falls were observed among some of the *ATM* or *PALB2* mutated cases, encouraging further studies in these populations. In the TOPARP-B validation set of the trial, 98 patients were treated after prospective selection based on NGS testing of a primary tumor or metastatic biopsy sample. Using the same composite response criteria as in the first stage of the study, the response rate in the validation set was 47% (43/92 evaluable patients), with a radiological response rate of 20% and a PSA50 response rate of 34%. Among the 30 evaluable patients with *BRCA1/2* mutations, the radiological response rate was 52% and the PSA50 response rate was 76%, leading to an 80% response rate following PCWG3 criteria (RECIST and/or PSA 50% fall), and 83% total when including CTC conversions, and a median radiographic progression-free survival (rPFS) of 8.3 months. In contrast, the RECIST/PSA response rate was 11% among the 19 patients with *ATM* mutations (37% composite response rate including CTC conversions) and a median rPFS of 5.8 months, or 0% among patients with *CDK12* mutations (25% of *CDK12* mutated cases achieved a CTC conversion but no radiological or PSA responses were observed) with a median rPFS of 2.9 months. Among cases with less common mutations, responses were seen in some patients harboring *PALB2*, *FANCA* and *CHEK2* mutations.

TRITON2 is a single-arm phase II trial that evaluated the antitumor activity of rucaparib in men with mCRPC and HRR gene mutations who had progressed to at

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least one novel hormonal agent and one line of taxane chemotherapy; TRITON2 led to the accelerated of rucaparib by the FDA in 2020 for patients with BRCA1/2 alterations (Abida *et al.* 2020). The primary endpoint was objective response based on RECIST v1.1 among patients with measurable disease. PSA50 response rate and rPFS were key secondary endpoints. A total of 115 patients with *BRCA1/2* alterations (*BRCA1* = 13, *BRCA2* = 102) were enrolled and treatment with 62 of these patients presenting measurable disease for the primary endpoint analyses. The radiological response rate among the *BRCA1/2* population was 51%, and the PSA50 response rate was 55%, with a median rPFS of 9.0 months. The trial also enrolled 78 patients with mutations in DDR genes beyond *BRCA1/2*. Radiographic or PSA responses rate was very limited in these subgroups: 2/19 (10.5%) and 2/49 (4.1%) radiological and PSA responses, respectively, among patients with *ATM* mutations, and only 1/15 (6.7%) PSA responses among patients with *CDK12* mutations or 2/12 (16.7%) among patients with *CHEK2* alterations. Responses were observed in cases harboring mutations in *PALB2, FANCA, BRIP1*, or *RAD51B*.

Talazoparib is a potent PARP inhibitor; the TALAPRO1 trial (de Bono *et al.* 2020*b*) assessed its antitumor activity among men with mCRPC progressing to taxanes and novel hormonal therapy (NHT), measurable soft tissue disease and a mutation in *ATM, ATR, BRCA1, BRCA2, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2* or *RAD51C*, using the FoundationOne CDx test in tumor tissue biopsies. With a similar design to the TRITON2 trial, the primary endpoint was objective response rate. In total, 128 patients were enrolled, with 104 being evaluable. Half of the evaluable population were patients with *BRCA2* alterations, whereas alterations in *BRCA1*, *ATM* or *PALB2* accounted for 4, 14 and 4% patients, respectively. Overall, the radiological response rate in the study was 30%. Similar to the findings of the TOPARP and TRITON2 studies, patients with *BRCA1/2* alterations were more likely to respond (46% radiological response rate, 66% PSA50 response rate, overall 72% composite response rate when including CTC conversions, to compare it with the TOPARP findings).

Last, the GALAHAD study is evaluating the antitumor activity of Niraparib in men with mCRPC and DDR gene alterations (Smith *et al.* 2020). The differential feature of this study is the use of a customized liquid biopsy NGS test for patient selection, with the trial eligibility demanding evidence of biallelic gene alterations. In all the other phase II trials of PARPi in mCRPC, finding a pathogenic mutation was sufficient to call a patient eligible, regardless of evidence of loss-of-heterozygosity or other means of second allele hits. Preliminary results reported are consistent with the response rates reported for other PARPi (Smith *et al.* 2020).

So far, only olaparib has been approved based on data from a randomized phase III trial. The PROFOUND study (de Bono *et al.* 2020*a*) evaluated olaparib in men with mCRPC who had disease progression while receiving a new hormonal agent (e.g. enzalutamide or abiraterone). All patients were selected based on central tumor tissue NGS testing and a panel of 15 HRR-related genes, using either archival or recent biopsy tissue from primary or metastatic disease. Among the 4858 samples tested, 83% were prostate biopsies, or material from prostate surgical procedures; the other, 7% were lymph node biopsies and the remaining 10% were metastatic biopsies, most commonly from bone lesions (de Bono *et al.* 2020*a*). Patients with mutations in at least one of the genes of interest were randomized to receive olaparib vs a control arm receiving a further new hormonal agent (abiraterone or enzalutamide, at investigator discretion). This randomization was stratified based on prior exposure to taxane chemotherapy (66% of patients had received at least one prior line with taxanes) and the presence of measurable soft tissue or visceral disease. The trial was structured around two cohorts: cohort A included 245 patients with mutations in *BRCA1, BRCA2* or *ATM*; cohort B included 142 patients with alterations in any of the 12 other prespecified genes in the study protocol (*BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D,* and *RAD54L*).

The primary endpoint was imaging-based PFS in patients with at least one alteration in *BRCA1, BRCA2*, or *ATM* (cohort A). In cohort A, imaging-based PFS was significantly longer in the olaparib group than in the control group (7.4 months vs 3.6 months). The trial also met the predefined threshold for the key secondary endpoint of OS, with a median OS of 18.5 months in the olaparib group and 15.1 months in the control group in cohort A, despite approximately 2/3 patients in the control arm crossed-over to olaparib treatment upon progression. In the exploratory cohort B, however, no significant differences in OS were observed. Exploratory gene subgroup analysis confirmed the key findings from the phase II trials of different PARP inhibitors, with patients harboring *BRCA1/2* alterations deriving the most benefit. The hazard ratios for rPFS in the *BRCA1/2*, *ATM* and *CDK12* altered subgroups was 0.22 (95% CI 0.12–0.32), 1.04 (95% CI 0.61–1.87) and 0.74 (95% CI 0.44–1.31), respectively; for OS, HR were 0.63

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(95% CI 0.42–0.95), 0.93 (95% CI 0.53–1.71) and 0.65 (95% CI 0.35–1.25) for patients with *BRCA1/2*, *ATM* and *CDK12* alterations, respectively. All the other 11 genes included in the companion diagnostic test, accounted together for only 61 patients in the PROFOUND trial; hence, it is not feasible to conduct individual-gene analysis for these small subgroups. Beyond the observed rPFS and OS benefit, olaparib was also consistently superior to the control arm for the different pain control and quality of life parameters analyzed in the study based on patient-reported questionnaires. The results from the PROFOUND trial have led to the approval of olaparib for men with mCRPC. In the US, the FDA registration accepts as selection biomarker mutations in any of 14 genes (*BRCA1, BRCA2, ATM*, *BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D,* and *RAD54L*); which represent all but one (PPP2R2A) genes included in the clinical trial companion biomarker test. PPP2R2A gene mutations were excluded from the approval based on emerging preclinical evidence of the less relevant role of that gene in HRR function, as well as the lack of efficacy observed for patients with PPP2R2A mutations in the PROFOUND trial. In Europe, contrarily, the EMA approval is restricted to patients with *BRCA1/2* alterations. In other countries, the approval also includes *ATM* mutations, reflecting the original design of cohort A of the study.

Currently, rucaparib is also being explored in a randomized phase III study, the TRITON3 trial (NCT02975934) (Ryan *et al.* 2018). In this case, the control arm includes abiraterone, enzalutamide or docetaxel at investigator's discretion. The target population initially was set to mCRPC patients with *BRCA1, BRCA2* or *ATM* alterations, although after the TRITON2 results, the study is now focusing on the *BRCA1/2* altered population.

## Predictive genomic biomarkers for PARPi treatment

The phase II and III trials of the different PARPi have demonstrated the antitumor activity of this drug class in advanced prostate cancer but have also raised concerns about the optimal gene set to include as selection biomarker. Across the different studies, data constantly shows that (1) responses are frequent and relatively durable among patients with *BRCA1/2* alterations; (2) responses are less common among patients with *ATM* or *CDK12* mutations, two genes not directly involved in the HRR pathway but involved in DSB regulation (Table 1), and (3) there is insufficient data to make any strong claim for low-prevalence gene subgroups, such as *PALB2, RAD50, RAD51, FANCA, FANCM*, BRIP1, as very few patients with these biomarkers were enrolled in the different PARPi clinical trials.

With regards to the first point, it seems clear that PARPi are a suitable therapeutic option for patients with *BRCA1/2* alterations. This is also supported by data from clinical trials in other tumor types. A separate question is when would PARPi treatment fits best in the natural history of the disease. In the PROFOUND trial, 2/3 of patients were enrolled in the study after having received taxane-chemotherapy, whereas 1/3 were taxane-naïve. An unplanned exploratory analysis suggests the benefit may be larger for those patients receiving olaparib upfront before chemotherapy; however, this is a common effect observed also for other targeted agents across diseases, including in prostate cancer. Only clinical trials testing different treatment sequences in a randomized fashion could answer this question.

On the other hand, most trials so far reported together results for patients with *BRCA1* and *BRCA2* mutations. However, it is necessary to highlight that *BRCA1*

**Table 1** Response rate, based on different clinical endpoints, for patients with *BRCA1/2* vs *ATM* mutations receiving single-agent PARP inhibitors in the reported phase II and III clinical trials.

| | **TOPARP-B** (Mateo *et al.* 2020*a*) | **PROFOUND** (Hussain *et al.* 2020) | **TRITON2** (Abida *et al.* 2020) | **TALAPRO1** (de Bono *et al.* 2021) |
|---|---|---|---|---|
| | Olaparib (%) | Olaparib (%) | Rucaparib (%) | Talazoparib (%) |
| BRCA1/2 | | | | |
| Radiological response rate | 52 | 44 | 51 | 46 |
| PSA response rate | 76 | 62 | 55 | 66 |
| CTC conversion rate | 77 | 69 | Not reported | 81 |
| Composite response rate | 83 | Not reported | Not reported | 72 |
| ATM | | | | |
| Radiological response rate | 8 | 10 | 11 | 12 |
| PSA response rate | 5 | 13 | 4 | 7 |
| CTC conversion rate | 50 | 40 | Not reported | 50 |
| Composite response rate | 37 | Not reported | Not reported | 24 |

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mutations are uncommon in prostate cancer, so most of the data reported to date come from patients with *BRCA2* mutations. As example, from 32 patients treated in the TOPARP-B trial, only 2 had *BRCA1* alterations compared to 30 with *BRCA2* alterations. Similar proportions apply to the TALAPRO1 (*BRCA2* = 57, *BRCA1* = 4) and TRITON2 (*BRCA2* = 102, *BRCA1* = 13) studies. In a recent retrospective look across trials, Markowski and Antonarakis observed a lower response rate in patients with *BRCA1* (vs *BRCA2*) alterations (Markowski & Antonarakis 2020). This differential effect may be linked to the observation that, while most *BRCA2* mutations associate with a biallelic loss, that does not seem to be the case for *BRCA1* mutations in prostate cancer (Sokol *et al.* 2020). As we pursue further stratification of metastatic prostate cancer for PARPi treatment based on gene-per-gene alterations, further attentions need to be paid to the particularities associated with *BRCA1* defects in prostate cancer.

Moreover, it is important to acknowledge not all patients with *BRCA2* alterations respond to PARPi, and even among those who respond, some of them develop resistance within less than 6 months. Possible mechanisms of resistance to PARP inhibition that have been proposed consist of reversion mutations in *BRCA2* and *PALB2*, restoring functional proteins and DNA repair (Goodall *et al.* 2017, Quigley *et al.* 2017). Preclinical studies of mechanisms of PARPi resistance, in parallel to emerging clinical data in prostate cancer and other disease, would be key for understanding and overcoming resistances through novel therapeutic approaches (Li *et al.* 2017*a*, Chen *et al.* 2019, Lombard & Gao 2020). As more data emerges from clinical trials, it is important to study both exceptional responders and non-responders to elucidate determinants of the different degrees of sensitivity. In this line, a recent retrospective analysis of biopsies collected in the TOPARP-B trial of olaparib in mCRPC showed that patients with homozygous deletions in *BRCA2* are more likely to achieve prolonged responses compared to patients with truncating mutation in *BRCA2*, regardless of their germline or somatic origin, possibly related to the different resistance mechanisms implicated in each case (Carreira *et al.* 2021).

A low response rate for patients with *ATM* and *CDK12* mutations has been consistently found across clinical trials of different PARPi. Still, some patients with *ATM* mutations do respond, and some present prolonged disease stabilizations or minor responses. It is difficult to dissect the prognostic vs predictive role of *ATM* mutations from single-arm phase II trials, but definitely further research, both in the laboratory as in the clinic, is needed to identify who are the patients with ATM mutations who may indeed benefit from PARPi therapy and design a more precise biomarker selection strategy for the ATM altered subgroup. One point that merits further study is the understanding of what ATM alterations truly lead to complete loss of function. On the one hand, discrepancies between mutational status and ATM protein expression, evaluated by immunohistochemistry, have been observed (Neeb *et al.* 2021); on the other hand, some ATM mutations detected in liquid biopsy tests and not present in tumor samples may be reflecting clonal hematopoietic events rather than true tumor alterations (Jensen *et al.* 2021).

Last, a significant challenge in the field is how to generate robust data to validate the predictive value of low-prevalence mutations in those genes in the 'long tail' of uncommon alterations (Armenia *et al.* 2018). Most of the trials so far pooled these mutations together, but this probably will only confound the validation of each of these biomarkers. It is likely that the relevance of mutations in genes such as *PALB2* or *RAD50*, at the core of the HRR process, is different to that of other indirect HRR regulators such as *CHEK2*. However, the low prevalence of these mutations makes it impossible for any of these trials to accumulate sufficient cases to pursue specific analysis. Metanalysis of these different studies may help, but as PARPi are now part of the clinical options for men with prostate cancer, it is imperative that prospective 'real-world' data registries capture these cases, toward building the necessary burden of data to pursue definitive gene-per-gene analyses.

## Can we refine patient selection by incorporating further biomarkers?

There are three main approaches to identifying HRR deficiency in tumor samples: first, the identification of HRR gene mutations, which has been used in most prostate cancer clinical trials of PARP inhibitors so far; secondly, the identification of genomic scars of HRR deficiency, repetitive patterns of imbalanced translocations, copy number changes and particular mutation signatures that accumulate as a result of the use of error-prone DSB systems in HRR defective tumors; and last, functional tests evaluating the capacity of the tumor to repair damage via homologous recombination.

The association of genomic signatures or scars with *BRCA1/2* alterations are well established in breast and ovarian cancer (Nik-Zainal *et al.* 2016, Davies *et al.* 2017, Miller *et al.* 2020). Quigley *et al.* confirmed the presence

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of these genomic signatures in *BRCA*-deficient prostate cancers (Quigley *et al.* 2018), and Sztupinszki *et al.* optimized the analysis pipelines to overcome some of the technical challenges to identify these signatures in FFPE biopsies (Sztupinszki *et al.* 2020). However, whole-genome or even whole-exome sequencing is yet far from clinical implementation due to the complex data analysis requirements. Hence, some targeted panel approaches have optimized the detection of some of the individual features defining these HRR deficiency signatures, making them feasible for clinical use. Two of these tests, the genomic instability score (GIS) and the percentage of the genome affected by sub-chromosomal loss-of-heterozygosity (gLOH), associate with benefit from PARP inhibitors in ovarian cancer, and there is hope they can help to refine patient selection strategies in prostate cancer too. However, clinical qualification of these biomarkers, specifically in prostate cancer studies, is needed. In a pan-cancer study, for example, Sokol *et al*. demonstrated that the distributions of gLOH values in *BRCA1/2* mutated and WT prostate cancer are different to ovarian cancer (Sokol *et al.* 2020).

Functional tests assessing the induction and nuclear location of key HRR effectors, such as RAD51, are still in early stages of development, but could be a powerful tool to identify HRR tumors in the clinic, offering also the advantage of being a 'live' maker of HRR function, contrarily to the genomic scars, which are permanent. Most of these tests need *ex vivo* incubation of the tumor samples with DNA damaging agents, such as radiation, making it challenging for clinical testing (Graeser *et al.* 2010, Hill *et al.* 2018) in recent years; however, tests that evaluate baseline damage and repair in FFPE biopsies are advancing clinical development in ovarian and breast cancer (Cruz *et al.* 2018, Eikesdal *et al.* 2021), and promising preliminary data has been reported from prostate cancer studies (Carreira *et al.* 2021).

Both genomic signatures and functional tests could eventually become complementary tools to NGS testing for optimizing patient stratification for PARPi treatment.

## Can drug combinations increase the indications of PARP inhibitors in prostate cancer?

The efforts for developing combinatory approaches to treatment with PARP inhibitors aim to either: (1) to delay the emergence of secondary resistance in patients with PARPi-sensitive tumors; and/or (2) to achieve meaningful antitumor effect in a wider population of patients with tumors that may be resistant to PARPi as monotherapy. Several combination strategies are at different stages of clinical development, many of them building from the learnings in ovarian cancer.

### Combinations with AR signaling inhibitors

The androgen receptor axis is the key driver of prostate cancer progression, as well as the main therapeutic target in this disease (Sharifi *et al.* 2010, Lepor & Shore 2012). The rational for co-targeting both the AR and DDR pathways are based on the crosstalk between them. In preclinical models, AR blockade resulted in downregulation of several DDR genes and upregulation of PARP1 (Asim *et al.* 2017, Li *et al.* 2017*b*). Non-homologous end-joining repair of DNA double-strand breaks (DSBs) is affected by ADT and PARP1 activity is increased as a function of prostate cancer progression (Asim *et al.* 2017). Despite these evidences, the exact mechanisms implicated in this crosstalk have not been completely elucidated.

A phase II trial of olaparib in combination with abiraterone acetate and prednisone has reported results (Clarke *et al.* 2018). In this study, patients with metastatic castration-resistant disease who previously had received docetaxel, were randomized 1:1 to receive abiraterone acetate and prednisone with olaparib or with placebo, without prior knowledge of genomic status for HRR genes. The investigational combination resulted in longer rPFS (primary endpoint of the trial), with a median rPFS of 13.8 months compared to 8.2 months in the placebo and abiraterone arm (hazard ratio 0.65, $P = 0.034$), at the expense of a higher prevalence of hematological, gastrointestinal and cardiovascular adverse events in the olaparib combination arm. A retrospective analysis of genomic profiles for the subset of patients with available tumor samples revealed that both groups of patients with or without HRR mutations seem to derive some benefit from the addition of olaparib. Based on these data, several phase III trials combining different PARP inhibitors with abiraterone acetate or enzalutamide have been launched; both in the mCRPC and in the metastatic hormone-naïve prostate cancer (mHNPC) settings (Table 2) (Agarwal *et al.* 2019, Clarke *et al.* 2019, Chi *et al.* 2020, Rao *et al.* 2021). These trials are expected to read out over the next couple of years and, collectively, should help toward better understanding the clinical value of this AR-DDR pathways crosstalk. As novel hormonal therapies are being moved toward the mHNPC space, it is very relevant to resolve open questions about the exact mechanisms by which these combinations may be synergistic, so not only we can refine the target population but also ascertain

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the optimal timing for combination treatment along the natural history of the disease.

Of note, prior to these studies, a randomized phase II trial with veliparib, a less potent PARP inhibitor, and abiraterone did not find significant differences in patient outcome: similar response rates and PFS were observed among 148 patients randomized to abiraterone and prednisone with or without veliparib. However, the trial was initially designed to interrogate the predictive value of *ETS* status with regards to response to the combination therapy; no significant differences based on *ETS* status were found (Hussain *et al.* 2018).

## Combinations with immune checkpoint inhibitors (ICI)

Over the last decade, the development of antibodies blocking immune checkpoints, such as programmed cell death 1 (PD-1), its ligand (PDL-1) and cytotoxic T lymphocyte antigen 4 (CTL-4), have significantly impacted the treatment standards for multiple types of cancers (Reck *et al.* 2016, Motzer *et al.* 2018, Larkin *et al.* 2019, Oaknin *et al.* 2020). In prostate cancer, however, the clinical benefit observed has been modest and restricted to a small number of patients. The combination of PARP inhibitors and ICI is being pursued in different tumor types under two main premises: on the one hand, under the hypothesis that HRR deficient tumors may result in increased neoantigen loads due to the accumulation of indels and frameshift mutations (Jiao *et al.* 2017, McGrail *et al.* 2018); on the other hand, dsDNA breaks accumulation as a result of PARP inhibition would result in the release of dsDNA outside the nucleus to the cell cytoplasmic space. It has been shown in preclinical models that the sensing of these dsDNA in tumor cells by cytosolic DNA sensor cyclic GMP-AMP synthase (cGAS) would lead to an increased activation of the interferon (IFN) genes (STING) signaling pathway (Ablasser *et al.* 2013). Several clinical trials combining PARP and immune checkpoint inhibitors are being pursued in prostate cancer. So far, only a small phase I/II trial ($n=17$) of olaparib plus durvalumab (NCT02484404) in men with mCRPC progressing to novel hormonal agents has reported full results, with a median rPFS of 16.1 months (95% CI 4.5–16.1 months). Most of the responses, as well as the most durable ones, were observed in men with *BRCA2* loss (Karzai *et al.* 2018).

## Combination with anti-VEGF therapies

Hypoxic conditions have been shown to impair synthesis of homologous recombination proteins *in vitro* (Bindra *et al.* 2005*a*, Bindra *et al.* 2005*b*, Chan *et al.* 2008); this effect would lead to a conditional HRR defect that can be exploited therapeutically with PARP inhibitors. This has been the premise for combining PARP inhibitors with antiangiogenic drugs in clinical trials, with successful results in ovarian cancer (Ray-Coquard *et al.* 2019, Lheureux *et al.* 2020). Preliminary results from a randomized phase II study combining olaparib plus cediranib, vs olaparib alone in men with mCRPC have been recently reported (McKay *et al.* 2021). The primary endpoint of the study was rPFS, which was clearly prolonged for patients receiving the combination compared to those receiving olaparib alone (8.47 months vs 3.97 months, $P=0.045$). A retrospective analysis of genomic profiling suggested the benefit of the combination was notable only in patients with DNA repair gene mutations, although the small sample size for each subgroup demands being prudent. Of note, VEGF

**Table 2** Ongoing phase III placebo-controlled trials of PARPi in combination with AR targeting agents in the mCRPC setting.

| PARPi | Combined AR agent | Population | Trial (identifier) | Primary outcome |
|---|---|---|---|---|
| Niraparib | Abiraterone acetate + prednisone | First line without prior docetaxel.<br>Cohort 1: mCRPC and HRR gene alteration<br>Cohort 2: mCRPC and No HRR gene alteration<br>Cohort 3: mCRPC | MAGNITUDE (NCT03748641) | rPFS by RECIST v1.1 and PCWG3 in HRRm and ITT population (hierarchical) |
| Olaparib | Abiraterone acetate + prednisone | First line without prior docetaxel in mCRPC | PROpel (NCT03732820) | rPFS by RECIST v1.1 and PCWG3 |
| Talazoparib | Enzalutamide | First line without prior docetaxel in mCRPC | TALAPRO-2 (NCT03395197) | rPFS by RECIST v1.1 and PCWG3 in HRRm and ITT population (co-primary) |
| Rucaparib | Enzalutamide | First line mCRPC. Prior docetaxel is allowed in HSPC setting | CASPAR (NCT04455750) | rPFS and OS (co-primary) |

CRPC, castration-resistant prostate cancer; HRR, homologous recombination repair; HSPC, hormone-sensitive prostate cancer; rPFS: radiographic progression-free survival; PCWG3: Prostate Cancer Working Group 3; pts: patients; HRR: homologous-recombination repair; ITT: intention-to-treat.

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inhibitors are highly active in ovarian cancer, whereas prior attempts combining antiangiogenic drugs and docetaxel in mCRPC have produced disappointing results (Kelly *et al.* 2012, Tannock *et al.* 2013, Michaelson *et al.* 2014, Petrylak *et al.* 2015).

### Combination with DNA damaging and other DDR targeting agents

The accumulation of DNA damage and increased replicative stress from PARP inhibitors and other DNA repair targeting agents, as well as DNA damaging agents can lead to unsustainable genomic instability and cell death (Haynes *et al.* 2018). The combination of PARP inhibitors with DNA damaging chemotherapies, such as platinum salts and alkylating agents, is challenging due to overlapping hematological toxicities. The combination of the PARPi veliparib and temozolomide was explored in a clinical trial, showing very modest activity in mCRPC (Hussain *et al.* 2014). Beyond PARP inhibitors, potent inhibitors of other key targets involved in the DDR, including ATR, ATM, CHK1/2, WEE1, and DNA-PK are in clinical development, and their combination is being explored, aiming to deliver enhanced antitumor activity (NCT03579316). In prostate cancer, radiopharmaceuticals targeting PSMA represent one of the most promising novel therapeutic in the development pipeline. PSMA-targeted small molecules bound to 177-Lutetium (177Lu) deliver high doses of beta-radiation after internalizing in the cancer cell, causing double-strand breaks (Hofman *et al.* 2018, Rahbar *et al.* 2018). As 177Lu-PSMA radioligands advance toward regulatory approval, clinical trials are beginning to explore the potential for combining them with PARP inhibitors (NCT03511664, NCT03042312, NCT03392428) (Calais *et al.* 2019, Sartor *et al.* 2020, Hofman *et al.* 2021).

## Conclusions

PARP inhibitors are active against advanced prostate cancer with HRR-associated gene mutations. Patients with germline or somatic *BRCA*2 alterations frequently achieve tumor responses, some of them of significant durability; responses have also been observed among patients with other HRR-associated gene mutations, although these are less common and typically of shorter duration; further study of these cases in prospective registries, validation of comprehensive genomic biomarkers and integration of preclinical studies and clinical data may help to better identify those patients beyond the *BRCA2*-mutated population who truly benefit from PARPi treatment, and would be key to validate the clinical relevance of low-prevalence mutations that have been poorly represented in the different clinical trials so far. Combination studies aiming to prolong benefit for PARPi-sensitive tumors as well to expand the potential target population are ongoing; however, these studies need to take into account for the hypothesized mechanism of action for each specific combination, in order to precisely identify the optimal target population for clinical development.

**Declaration of interest**

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**Author contribution statement**

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