PARP Inhibitors in Prostate Cancer: Practical Guidance for Busy Clinicians

David J. VanderWeele, MD, PhD, and Maha Hussain, MD

Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, Illinois

Corresponding author:
Maha Hussain, MD
Genevieve Teuton Professor of Medicine
Robert H. Lurie Comprehensive Cancer Center
Northwestern University
303 E Superior St, Ste 3-107
Chicago, IL 60611
E-mail: maha.hussain@northwestern.edu
Tel: (312) 908-5487
Fax: (312) 908-1372

Abstract: The management of prostate cancer entered a new era of biomarker-driven therapy in May of 2020, when the US Food and Drug Administration (FDA) approved the poly(ADP-ribose) polymerase (PARP) inhibitors rucaparib and olaparib as the first targeted therapies in biomarker-preselected patients with metastatic castration-resistant prostate cancer. This approval provided new options for patients with deleterious *BRCA1* or *BRCA2* mutations (olaparib and rucaparib), or with deleterious mutations in one of a number of homologous recombination repair genes (olaparib). Compared with either enzalutamide or abiraterone, olaparib demonstrated an overall survival benefit in men with metastatic castration-resistant prostate cancer who had disease progression while receiving enzalutamide and/or abiraterone. Additional PARP inhibitors are currently being evaluated as monotherapy. The data are strongest for alterations in *BRCA2*; alterations in other genes are associated with less benefit or occur less frequently. To date, tissue DNA remains the gold standard for identifying predictive mutations, but sequencing from tissue DNA fails to provide a result in approximately 30% of cases. Biopsies of metastatic sites are more likely to yield results and more likely to identify predictive alterations. Plasma-based sequencing platforms are also approved by the FDA, and they appear to provide a result in most patients with late-stage disease. The best way and time to evaluate for the presence of selection biomarkers are not firmly established, but patients whose disease has progressed on androgen deprivation therapy should be evaluated. PARP inhibitors are also being studied in combination with other therapies, such as AR-targeted therapies, immunotherapies, and radiation, among others, in unselected patients.

Keywords
Metastatic castration-resistant prostate cancer; olaparib, PARP inhibitors, rucaparib

Introduction: The Biology of PARP Inhibition

Carriers of *BRCA1* or *BRCA2* deficiency (eg, *BRCA2* +/–) are predisposed to the development of a number of different types of cancer, including breast, ovarian, prostate, and pancreatic cancers (known as breast and ovarian cancer syndrome, or BOCS). The resulting

tumors lose the second copy of the allele (eg, *BRCA2* –/–) and thus are deficient in homologous recombination repair (HRR).[1] Although this DNA repair defect likely contributes to an accelerated accumulation of mutations, it also presents a therapeutic vulnerability.

Poly(ADP-ribose) polymerase (PARP) binds DNA at sites of single-strand breaks to facilitate repair. PARP inhibitors trap PARP on the DNA and block its catalytic activity. This process removes a complementary avenue of DNA repair and is synthetically lethal in combination with the genetic DNA repair defect.[2] Restoration of the functional gene abrogates sensitivity to PARP inhibitors, confirming that it is the genetic DNA repair deficiency that is responsible for sensitivity to PARP inhibition.[3] Because only tumor cells harbor this defect (tumor cells are homozygous-deficient; other cells remain heterozygous), PARP inhibitors are tumor-specific, with a relatively broad therapeutic window and tumor efficacy even in patients who are heavily pretreated.[4]

Like people with BOCS, patients who lose both copies of *BRCA1* or *BRCA2* or other genes involved in HRR through somatic loss also stand to benefit from PARP inhibition.

In the first large description of the genomic landscape of advanced prostate cancer, the Stand Up To Cancer (SU2C) Prostate Cancer Foundation Prostate Dream Team performed integrative genomics on biopsy specimens from 150 individuals with metastatic prostate cancer. Nearly all patients had an identifiable driver mutation. Even when alterations in the androgen receptor gene were not considered, 65% of cases harbored a putatively clinically actionable alteration. This included 19% of individuals with alterations in the DNA repair pathway.[5] In May 2020, clinical action based on DNA repair alterations became possible when the US Food and Drug Administration (FDA) approved the PARP inhibitors rucaparib (Rubraca, Clovis Oncology) and olaparib (Lynparza, AstraZeneca) as the first targeted therapies in biomarker-preselected patients with metastatic castration-resistant prostate cancer (mCRPC).

Trials of PARP Inhibitor Monotherapy

TOPARP-A was the first clinical trial that systematically evaluated a PARP inhibitor in prostate cancer (Table 1).[6] This was a single-arm, phase 2 study in which 50 patients with mCRPC that had progressed on prior chemotherapy received olaparib treatment at 400 mg twice daily. Of 49 evaluable patients, 16 (33%) had a response (composite endpoint), with an average duration of treatment in the responders of 40 weeks. Sequencing was done on tumor biopsy specimens or archival tissue, with biomarker positivity defined as inactivation of a gene involved in HRR. Of 16 patients who were classified as biomarker-positive, 14 (88%) had a response to olaparib, with a median radiographic progression-free survival (rPFS) of 9.8 months. Of 34 patients who were biomarker-negative, 2 had a response (median rPFS, 2.7 months).

Trials Leading to FDA Approvals

PROfound. The emerging data from the SU2C study on the rate of HRR mutations in advanced prostate cancer,[5] coupled with data from TOPARP-A on the efficacy of olaparib in biomarker-positive patients[6] and the benefit of PARP inhibitors in breast and ovarian cancer,[7-9] led to the design of the PROfound trial. Patients enrolled in PROfound had mCRPC that had progressed on prior therapy with either abiraterone and/or enzalutamide (Xtandi, Astellas). Patients had a deleterious or suspected deleterious alteration in 1 of 15 prespecified genes involved in HRR. In this randomized, open-label crossover trial, patients received either olaparib at 300 mg twice daily or the prespecified physician's choice of abiraterone or enzalutamide. Patients with a mutation in *ATM*, *BRCA1*, or *BRCA2* were in cohort A, and patients with mutations only in 1 of the other 12 genes (*BRIP1*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D,* and *RAD54L*) were in cohort B.

The PROfound trial met its primary endpoint, improvement in rPFS in cohort A, with a hazard ratio (HR) of 0.34 (median rPFS, 7.4 vs 3.6 months; 95% CI, 0.25-0.47; $P<.001$). It also demonstrated improvement in rPFS in cohorts A + B, with an HR 0.49 (median rPFS, 5.8 vs 3.5 months; 95% CI, 0.38-0.63; $P<.001$).[10] Despite the crossover, overall survival (OS) was 19.1 vs 14.7 months in cohort A (HR, 0.69), 14.1 vs 11.5 months in cohort B, and 17.3 vs 14.0 months in the overall population (A+B). A sensitivity analysis that adjusted for crossover showed HRs of 0.42, 0.79, and 0.76, respectively.[11] In evaluable patients in cohort A, the confirmed objective response rate (ORR) was 33% in the olaparib group and 2% in the control group. This trial led to FDA approval of olaparib for adult patients with deleterious or suspected deleterious germline or somatic HRR gene-mutated mCRPC that has progressed following prior treatment with enzalutamide or abiraterone. PROfound was the first positive biomarker-selected phase 3 trial in prostate cancer, establishing a new benchmark in the management of this disease.[10]

TRITON2. The TRITON2 trial was a single-arm phase 2 trial of rucaparib at 600 mg twice daily for patients with a mutation in *BRCA1*, *BRCA2*, or 1 of 13 other DNA damage repair genes whose disease had progressed on prior AR-targeted therapy and taxane-based chemotherapy.[12] Among 115 patients with a *BRCA1* or *BRCA2* mutation, the confirmed prostate-specific antigen

Table 1. Trials of PARP Inhibitor Monotherapy

Trial	Design	Arms	Eligibility	Diagnostic Tests	Efficacy
PROfound (NCT02987543)	Randomized, phase 3, open-label	Olaparib vs abiraterone + prednisone or enzalutamide	mCRPC, progressed after prior ARPI Cohort A: *BRCA1, BRCA2, ATM* Cohort B: 12 other HRR genes	Tissue, centrally analyzed	Cohort A: rPFS 7.4 vs 3.6 mo, cORR 33.3% vs 2.3% Cohorts A+B: rPFS 5.8 vs 3.5 mo
TRITON2 (NCT02952534)	Single-arm, phase 2	Rucaparib	mCRPC, progressed after prior ARPI and taxane; 1 of 15 HRR genes	Tissue or blood, local or central testing	ORR 44% in *BRCA1/2*, 0%-14% in non-*BRCA1/2*
TOPARP-A (NCT01682772)	Single-arm, phase 2	Olaparib	mCRPC, progressed after 1-2 chemotherapy regimens	Tissue	RR 33% in overall population, 88% in biomarker-positive patients
TOPARP-B (NCT01682772)	Randomized, phase 2	Olaparib 400 mg, olaparib 300 mg	mCRPC, progressed after 1-2 chemotherapy regimens; alteration in DDR gene	Tissue	RR 54% in 400-mg cohort, 39% in 300-mg cohort
GALAHAD (NCT02854436)	Single-arm, phase 2	Niraparib	mCRPC, progressed after ARPI and taxane for mCRPC; *BRCA1/2, ATM, FANCA, PALB2, CHEK2, BRIP1, HDAC2*	Plasma	ORR 41% in *BRCA1/2*, 9% in non-*BRCA1/2*
TALAPRO-1 (NCT03148795)	Single-arm, phase 2	Talazoparib	mCRPC, progressed after ARPI and taxane for mCRPC; *ATM, ATR, BRCA1/2, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C*	Gene panel	ORR 54.7% in *BRCA1/2*, 4%-22.7% in non-*BRCA1/2*

ARPI, androgen receptor pathway inhibition; cORR, confirmed objective response rate; DDR, DNA damage repair; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; mo, months; ORR, objective response rate; PARP, poly(ADP-ribose) polymerase; rPFS, radiographic progression-free survival; RR, response rate.

(PSA) response rate (decline in the PSA level of 50% or more) was 54.8%, and the overall response rates on independent radiology review and as assessed by investigators were 43.5% and 50.8%, respectively. TRITON2 led to accelerated FDA approval of rucaparib for patients with deleterious germline or somatic *BRCA* mutations who previously had been treated with AR-targeted therapy and taxane-based therapy.

Other Monotherapy Trials

Based on the observations from TOPARP-A, TOPARP-B was a follow-up phase 2 trial that enrolled 98 patients with mCRPC and a mutation in a DNA damage repair gene. Patients were randomly assigned to olaparib at 400 or 300 mg twice daily.[13] A confirmed composite endpoint (radiologic objective response, PSA response, and conversion of circulating tumor cell count) was observed in 54.3% of patients in the 400-mg arm and 39.1% of patients in the 300-mg arm. The genes most commonly mutated were *BRCA2* (31%), *ATM* (21%), and *CDK12* (21%). Doses were reduced in 37% of patients in the 400-mg arm and 12% of those in the 300-mg arm.

The PARP inhibitor niraparib (Zejula, GSK/Tesaro) has been evaluated in the single-arm phase 2 GALAHAD study.[14] Patients must have had disease progression on prior AR-directed therapy and a taxane, and they must have had bi-allelic alterations in *BRCA1* or *BRCA2* or 1 of 6 other genes. At the prespecified interim analysis, for patients with a *BRCA1* or *BRCA2* inactivation, the ORR was 41% (primary objective), the composite response rate

was 63%, and rPFS was 8.2 months. For patients with inactivation in one of the other genes, the ORR was 9% (both responses in patients with *FANCA* inactivation), the composite response rate was 17%, and median rPFS was 5.3 months.

The single-arm phase 2 TALAPRO-1 trial is evaluating talazoparib (Talzenna, Pfizer) in patients with disease progression on prior new hormonal therapy and who have received a taxane-based chemotherapy regimen.[15] Patients must have measurable disease and a mutation in *BRCA1*, *BRCA2*, or 1 of 9 other DNA damage repair genes. At interim analysis, the ORR was 28%. In patients with a *BRCA1* or *BRCA2* mutation, the ORR was 54.7% and the median rPFS was 9.3 months.

Practical Considerations

Samples Used for Biomarker Selection

Biomarker selection in the PROfound trial was based on the sequencing of tissue DNA. Overall, 4425 patients underwent screening. Of the samples from the 4047 patients who provided tissue for testing, 2792 (69%) were successfully sequenced with a biomarker outcome reported; in 8%, multiple tissue submissions were required to obtain a result.[16] Most samples (84%) were from a primary tumor. On a per-sample level, the success rate was 57% in archived samples and 64% in newly collected samples; the success rate was 56% for primary tissue vs 64% for metastatic tumors. The success rate was 52% with core needle biopsy and 74% with radical prostatectomy. Lymph node biopsies led to testing success 75% of the time, and the success rates for lung, liver, prostate, and bone biopsies were 61%, 56%, 56%, and 43%, respectively. The disparity between the success rate with soft tissue biopsy and that with bone biopsy is consistent with the SU2C West Coast Prostate Cancer Dream Team effort, in which lymph node biopsy led to successful transcriptome analysis in 63% of cases and bone biopsy in 36% of cases.[17] The yield from bone biopsy specimens tends to be higher when the biopsies are performed in areas of radiolucency, in areas of low attenuation, in lesions with ill-defined margins, and when metastases are sampled at the periphery.[18,19] It is critical to success with bone biopsies to obtain multiple core needle samples, fix them with formalin, and embed them in one paraffin block to maximize the likelihood of a successful pathology review. To enable genomic analyses, it is critical to avoid strong acid decalcification of bone biopsy specimens; for newly collected bone samples, the recommendation is that decalcification not be performed.

Of the tissue samples with a successful result, 28% had a mutation in a qualifying gene, and the prevalence of HRR mutations in the genes included in cohort A was 17%.[20] The rates of HRR mutation differed somewhat according to whether the tissue sequenced was primary tissue (27%) or derived from a metastatic site (32%). The genes most commonly altered were *BRCA2* (8.7%), *CDK12* (6.3%), and *ATM* (5.9%). In 2.1% of patients, co-occurring genes were mutated.

Ideally, patients who are classified as biomarker-positive have a loss of HRR function in all tumor cells, making all tumor cells sensitive to PARP inhibition. Mutations in DNA damage repair genes are thought to be driver mutations and occur early, which is consistent with the primary tissue having been predictive of response in PROfound. Genetic heterogeneity is found within the prostate, however, both between tumor foci and even within a dominant focus.[21-23] This heterogeneity may confound biomarker evaluation if a primary tissue biopsy captures a subclonal event not relevant to metastatic disease. Moreover, additional alterations can accumulate as disease progresses.[24,25] This appears to affect some genes (eg, *ATM*) more than others (eg, *BRCA2*). Consistent with the idea of an evolving genome is the higher rate of HRR mutation detection in metastatic disease (32%) than in primary disease (27%).

Many patients with advanced prostate cancer have high levels of circulating tumor DNA (ctDNA) in their plasma, which can be evaluated as a liquid biopsy to detect mutations in tumor DNA. It can be argued that ctDNA is more representative of the entire burden of disease in the body than is a sample from an individual metastatic site. However, the percentage of ctDNA in the cell-free DNA in plasma must be sufficiently high if it is to be reliably detectable. It appears that most patients with mCRPC and a PSA level greater than 10 ng/mL have sufficient ctDNA to enable the capture of mutations detectable in tissue biopsy, and sometimes ctDNA appears to be more sensitive than tissue.[26,27]

Similar to the results in PROfound, 888 of 1311 patients who submitted tissue for TRITON2 (68%) had a successful sequencing result, suggesting that one can expect a failure rate of approximately 30% with sequencing from tissue.[28] In contrast, 620 of 638 patients with plasma submitted (97%) were considered to have a successful sequencing result. No large data sets are available for a formal comparison of the clinical utility of tissue vs plasma sequencing. However, the TRITON2 study included next-generation sequencing analysis of tissue and/or plasma, with both local and central testing, and a subset of patients (161) had both tissue and plasma evaluated. Within that subset, 34 patients had an identified *BRCA1* or *BRCA2* mutation, and in 25 of these 34 (74%), the mutation was identified by both tissue and plasma sample. In an additional 15%, the mutation was identified by plasma alone, and in 12% by tissue but not plasma.

In general, a greater number of alterations were detected in plasma samples than in tissue samples, consistent with increased sensitivity from liquid biopsy. In August 2020, the FDA approved FoundationOne Liquid CDx, a pan-tumor liquid biopsy test for patients with solid tumors, as a companion diagnostic to identify patients who might benefit from rucaparib.[29] Larger data sets are needed to determine if biomarker detection from plasma is as predictive of response as biomarker detection from tissue.

Timing of Biomarker Evaluation

The PROfound study evaluated olaparib in patients whose disease had progressed on AR-targeted therapy and allowed the inclusion of patients with disease progression on a prior taxane. Of those randomized, 66% had received prior chemotherapy, including 20% who had received both docetaxel and cabazitaxel (Jevtana, Sanofi-Aventis). The TRITON2, TOPARP, GALAHAD, and TALAPRO-1 trials all required prior chemotherapy. The indication for olaparib is for the treatment of mCRPC after progression on AR-targeted therapy, and the indication for rucaparib is for the treatment of mCRPC after progression on prior AR-targeted therapy and chemotherapy. PARP inhibitor monotherapy continues to be explored in patients with HRR deficiency in other settings, including earlier-stage disease. Currently, however, the earliest FDA-approved indication for PARP inhibitor therapy is after progression following enzalutamide or abiraterone. It is reasonable, then, to obtain molecular testing while patients are on AR-targeted therapy, or as their disease is progressing, to determine if PARP inhibitor therapy is a treatment option. In support of this idea, the PROfound trial showed a higher rate of biomarker detection when a metastatic biopsy specimen was evaluated than when primary tissue was submitted, so it is possible that a later evaluation with metastatic tumor tissue would be more likely to detect an HRR mutation than an evaluation earlier in the disease course.

The National Comprehensive Cancer Network (NCCN) Guidelines recommend testing for HRR mutation in all patients with metastatic prostate cancer and to consider such testing in patients with regional disease.[30] No discussion of prior lines of therapy is included. Molecular testing early in the disease course, at the time metastatic disease appears, should uncover driver mutations already present. Supporting this, one would expect those patients with late-occurring or heterogeneous loss of homologous recombination function to have a relatively modest response to PARP inhibition. An added benefit of early molecular evaluation is that a delay in obtaining results to inform management decisions after progression on therapy can be avoided. This may be especially important for patients with particularly aggressive disease.

Gene-Level Responses

The strongest evidence of predictive value is for mutations in the *BRCA1* and *BRCA2* genes. Patients who have mutations in these genes are often the primary analysis cohort, with patients having additional genes comprising secondary or exploratory cohorts. For example, in the PROfound trial, cohort A comprised patients with *BRCA1*, *BRCA2*, or *ATM* gene mutations. This was the primary analysis cohort. Cohort B comprised patients with mutations in an additional 12 genes. Validating this grouping, the HR for rPFS was 0.34 in cohort A vs 0.49 in cohorts A and B. Similarly, in the TRITON2 trial, the ORR for patients with a *BRCA1* or *BRCA2* mutation was 43.5%. Among patients with mutations in other homologous recombination genes, only 7 confirmed responses were noted in 52 patients (13%). In TOPARP-B, the composite overall response rate for *BRCA1/2* was 83%; the next highest was 57% for *PALB2*.[13] These percentages appear to establish *BRCA1* and *BRCA2* as the genes most likely to predict response.

BRCA1 and *BRCA2* may not be equivalent predictive genes, however.[31] For example, in PROfound, rPFS with olaparib (10.83 months) in patients with *BRCA2* mutations was 3 times longer than rPFS with control (3.48 months). For patients with *BRCA1* mutations, the benefit was significantly less (2.07 vs 1.84 months). Similarly, the pooled ORR is 26.3% in *BRCA1* patients vs 50% in *BRCA2* patients when TOPARP-A, TOPARP-B, PROfound, TRITON2, and TALAPRO-1 are evaluated. Thus, *BRCA2* appears to be the gene most strongly predictive of response to PARP inhibition.

Debate regarding the efficacy of PARP inhibition in patients with *ATM* alterations has been significant. In the TOPARP-A trial, 4 patients with *ATM* alterations had a response, and only 1 did not.[6] In the PROfound trial, *ATM* alterations were included in the primary analysis cohort (cohort A).[10] More recently, however, doubt has been cast on the extent of benefit from PARP inhibition given an *ATM* alteration.[32] In PROfound, the rPFS for patients who had *ATM* alterations was 5.36 months with olaparib vs 4.7 months with control. In TRITON2, of 19 patients with measurable disease and an *ATM* alteration, 2 (10.5%) had a partial response. Among a total of 49 patients in with an *ATM* alteration, only 2 had a PSA response.

Inactivation of the *CDK12* gene has been proposed to predict benefit from PARP inhibition as well as immunotherapy. A multi-institution cohort of patients with *CDK12* alterations was found not to benefit from PARP inhibition.[33] In TRITON2, 0 of 10 patients with measurable disease and a *CDK12* alteration had an imaging

response, and 1 of 15 had a PSA response lasting 1.8 months. In PROfound, however, some indication of benefit was noted; rPFS with olaparib was 5.09 months vs 2.20 months with control.

Additional genes appear to be predictors of PARP inhibitor response, although the evidence is limited owing to the low frequency of alterations in these genes. In PROfound, 5 patients had *RAD51B* alterations and 5 had *RAD54L* alterations, and in both groups, rPFS was 3 times longer with olaparib than with control. One patient in TRITON2 with an *RAD51B* alteration had a partial response and a deep PSA response. The one patient with an *RAD54L* alteration did not have a response. On the other hand, patients with a *PALB2*, *FANCA*, or *BRIP1* alteration had radiographic and/or PSA responses. In TOPARP-B, the composite response for *PALB2* was 57%, with a radiographic response rate of 33.3%.[13]

The cause of the differences in response rates in different trials is not clear. Although it is generally thought that a class effect exists with PARP inhibitors, they differ in their binding properties. In addition, the studies used different methods to evaluate for biomarkers. For example, GALAHAD used a plasma-based assay, PROfound used a tissue-based assay, and TRITON2 used a combination of the 2, with both local and central review. Although it is generally thought that both copies of a gene need to be altered for a patient to benefit significantly from PARP inhibition, owing to the limits of biomarker assays, most studies have generally required only a single allele to be altered for trial eligibility. Finally, the completed studies have had different eligibility criteria, with earlier lines of therapy allowed in PROfound than in the other trials. All these factors preclude meaningful cross-trial comparisons.

Expected Toxicities

The synthetic lethality that exists between PARP inhibition and loss of HRR makes tumor cells far more sensitive to PARP inhibition than benign cells with intact HRR. Nonetheless, significant toxicities are seen. In PROfound, the only trial randomizing patients to PARP inhibition or control, 22% of patients receiving olaparib vs 4% of patients in the control arm (receiving abiraterone or enzalutamide) required a dose reduction because of an adverse event.[10] Similarly, 18% vs 8% required drug discontinuation because of an adverse event. The most common toxicities of any grade were anemia, nausea, and fatigue or asthenia.

In TRITON2, anemia, asthenia or fatigue, and thrombocytopenia were the grade 3 or higher toxicities noted in more than 5% of patients with non-*BRCA1* or non-*BRCA2* alterations[34]; alanine aminotransferase/aspartate transaminase increases also occurred in 5% of patients with *BRCA1* or *BRCA2* alterations.[12] In PROfound, anemia was the only grade 3 or higher toxicity that occurred in 5% or more of patients: 21% of patients in the olaparib arm vs 5% in the control arm.[10]

Combination Therapy With PARP Inhibition

PARP inhibition is also being explored in combination with other therapies in unselected and selected patients. In addition to its role in DNA repair, PARP promotes prostate cancer growth, in part through cooperation with the AR. PARP has a well-known role in the repair of DNA damage. Significantly, PARP also has a role in transcriptional control. This role promotes AR function, enhancing the binding of AR to chromatin and its transcriptional regulatory function.[35] The initial report of this relationship demonstrated that in prostate cancer models, PARP inhibition does not have a significant anti-tumor effect unless AR is present. Moreover, PARP inhibition works together with castration or other AR targeting.[35] A more focused evaluation of the role of PARP in transcription demonstrated that PARP regulates the transcription of genes previously found to be enriched in mCRPC.[36] This work highlights the role of PARP in transcriptional regulation, a role traditionally associated with AR. Others have demonstrated the converse, that AR plays a role in DNA damage repair. In both hormone-sensitive[37] and castration-resistant[38] prostate cancer, the AR regulates the transcription of DNA repair machinery. AR inhibition decreases the ability to repair DNA, increases tumor DNA "BRCA-ness," and leads to synthetic lethality with PARP inhibition.

Preclinical data suggest that the TMPRSS2-ERG gene fusion product, commonly found in prostate cancer, interacts with PARP and with DNA-dependent protein kinase, catalytic subunit (DNA-PKcs), and that cancers expressing ETS fusions are sensitive to PARP inhibition.[39] In NCI 9012, unselected patients with mCRPC received abiraterone alone or with veliparib, with randomization done according to ETS fusion status. The addition of veliparib did not affect response, nor did ETS status predict benefit from veliparib. Patients with DNA repair deficiency, however, were found to have improved PFS irrespective of their treatment arm.[40] This observation led to a follow-up trial evaluating single-agent therapy vs the combination of olaparib and abiraterone (NCT03012321).

In another randomized phase 2 trial in unselected patients with advanced mCRPC, abiraterone was given with or without olaparib (NCT01972217; Table 2).[41] The rPFS was 13.8 months in the olaparib arm vs 8.2 months in the placebo arm (HR, 0.65; *P*=.034). In both biomarker-positive and biomarker-negative patients, rPFS was improved with olaparib. On the basis of these encouraging results, 4 phase 3 trials are evaluating a

Table 2. Selected Trials of Combinations of PARP Inhibitors and AR Pathway Inhibitors

Trial	Design	Arms	Eligibility	Efficacy, Reported or Planned
NCI 9012 (NCT01576172)	Randomized, phase 2	Abiraterone +/– veliparib	mCRPC, <3 prior chemotherapies; randomized by *ETS* fusion status	PSA RR: 63.9% with abiraterone; 72.4% with abiraterone + veliparib
D081DC00008 (NCT01972217)	Randomized, double-blind, phase 2	Abiraterone + olaparib or placebo	mCRPC, prior docetaxel	Median rPFS: 13.8 vs 8.2 mo in overall population; 17.8 vs 6.5 mo in HRRm
TALAPRO-2 (NCT03395197)	Randomized, double-blind, phase 3	Enzalutamide + talazoparib or placebo	mCRPC, no prior ARPI or taxane for mCRPC	Primary: rPFS in unselected patients; rPFS in those harboring DDR deficiency
PROpel (NCT03732820)	Randomized, double-blind, phase 4	Abiraterone + olaparib or placebo	mCRPC, no prior abiraterone, no prior ARPI within 12 mo	Primary: rPFS
MAGNITUDE (NCT03748641)	Randomized, double-blind, phase 5	Abiraterone + niraparib or placebo	Metastatic prostate cancer; no prior therapy for mCRPC except <4 mo of abiraterone	Primary: rPFS
CASPAR (NCT04455750)	Randomized, double-blind, phase 6	Enzalutamide + rucaparib or placebo	First-line mCRPC	Primary: rPFS, OS
BRCAaway (NCT03012321)	Randomized, phase 2	Abiraterone vs olaparib vs abiraterone + olaparib (primary cohort); olaparib (exploratory cohort)	First-line mCRPC with altered A*TM* or *BRCA1/2* (primary cohort) or 1 of 17 other DNA repair genes	Primary: PFS

AR, androgen receptor; ARPI, androgen receptor pathway inhibition; DDR, DNA damage repair; HRRm, homologous recombination repair mutated; mCRPC, metastatic castration-resistant prostate cancer; mo, months; OS, overall survival; PARP, poly(ADP-ribose) polymerase; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival; RR, response rate.

PARP inhibitor in combination with an AR pathway inhibitor in the first-line setting for unselected patients with mCRPC. Both niraparib (NCT03748641) and olaparib (NCT03732820) are being combined with abiraterone, and talazoparib (NCT03395197) and rucaparib (NCT04455750) are being combined with enzalutamide.

The DNA damage resulting from PARP inhibition is hypothesized to increase the expression of neoantigens. On the basis of this theory, PARP inhibitors are being combined with immunotherapy to enhance the immune response. In a single-arm trial in unselected patients, the combination of olaparib and durvalumab (Imfinzi, AstraZeneca) achieved a higher-than-expected response rate (53%).[42] Response was more likely in patients with fewer peripheral myeloid-derived suppressor cells and with alterations in DNA damage repair genes. Olaparib and pembrolizumab (Keytruda, Merck) are being compared with abiraterone or enzalutamide in a phase 3 trial of unselected patients (NCT03834519).

Finally, given that radiation also induces DNA damage, several trials are evaluating PARP inhibition and radiotherapy administered through various routes. Under study are olaparib and radium (NCT03317392), as well as niraparib and radiotherapy (NCT04037254, NCT04194554).

Conclusion

PARP inhibitors have become the first targeted therapy approved by the FDA for biomarker-selected patients with advanced prostate cancer. The best way and time to evaluate patients for the presence of selection biomarkers are not firmly established, but most patients with disease progression on AR-targeted therapy should be evaluated. The current approval is for monotherapy in the second-line setting or later. However, the promising results with PARP inhibitors have led to the design of numerous trials looking at new settings (earlier stages of disease) and new strategies (potentially synergistic combination therapies). Results from phase 2 trials suggest that some of these strategies are likely to be successful, with broader indications for PARP inhibitors to come.

Disclosures

Dr VanderWeele has served on the advisory board of Clovis Oncology, and Dr Hussain has served on the advisory board of and has received honoraria for lectures from AstraZeneca. Their institution has received clinical trial funding from AstraZeneca.

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