Editorial Commentary

Rucaparib for metastatic castration-resistant prostate cancer: did TRITON3 deliver a trifecta?

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In May 2020, the U.S. Food and Drug Administration (FDA) authorized the biomarker-guided use of two poly-ADP ribose polymerase inhibitors (PARPi)—olaparib (1) and rucaparib (2)—for the treatment of metastatic castration-resistant prostate cancer (mCRPC). Approval was based on the results of the PROfound (3) and TRITON2 (4) studies, respectively, and marked the growing use of molecularly targeted therapies in this disease. Herein, we review the recently reported TRITON3 study (5)—a phase III study assessing rucaparib against physician's choice as second line therapy in mCRPC. We discuss the implications of this study within the current treatment landscape and review the use of biomarkers for selecting patients likely to respond to PARPi therapy in mCRPC.

The TRITON3 study was a randomized phase III trial that evaluated rucaparib (administered at a dose of 600 mg orally twice daily) compared to physician's choice of docetaxel, abiraterone, or enzalutamide in patients with chemotherapy-untreated mCRPC. Key eligibility criteria included confirmed progression after treatment with one second-generation androgen-receptor pathway inhibitor (ARPI) and the presence of a germline or somatic pathogenic alteration in either *BRCA1*, *BRCA2* or *ATM*. A total of 4,855 patients were screened for a final cohort of 405 patients. The majority of exclusions (n=4,340) were due to the absence of a qualifying genetic alteration. Patients were randomized (2:1) into either the rucaparib arm (n=270) or the control arm (n=135). The study design included two pre-defined primary endpoints, assessed in a step-down approach. The first was radiographic progression-free survival (PFS) in the *BRCA*-mutated group (those with *BRCA1* or *BRCA2* mutations), followed by PFS in the entire intent-to-treat (ITT) population that also included *ATM* alterations.

In the *BRCA*-mutated group, patients in the rucaparib arm had a PFS of 11.2 months [95% confidence interval (CI): 9.2–13.8], compared to 6.4 months (95% CI: 5.4–8.3) in the control group. This resulted in a significant hazard ratio (HR) of 0.50 (95% CI: 0.36–0.69; P<0.001). For the entire ITT population, the median PFS was 10.2 months (95% CI: 8.3–11.2) in the rucaparib group and 6.4 months (95% CI: 5.6–8.2) in the control group, yielding a HR of 0.61 (95% CI: 0.47–0.80; P<0.001). A key secondary endpoint was overall survival (OS), although the data remains immature at this point. Within the *BRCA*-mutated group, 54% (162 out of 302) of patients had died at the time of data analysis. The median OS was 24.3 months (95% CI: 19.9–25.7) in the rucaparib group and 20.8 months (95% CI: 16.3–23.1) in the control group, showing no statistical significance (HR, 0.81; 95% CI: 0.58–1.12; P=0.21).

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Notably, the study allowed for crossover, with 47% (63 out of 135) of patients in the control group eventually receiving rucaparib post-progression. Objective responses, defined as radiological complete or partial responses in patients with measurable disease at baseline, were observed in 45% (37/82) of BRCA-mutated patients treated with rucaparib, versus only 16% (9/55) in the control group.

A significant aspect of the TRITON3 study was the inclusion of docetaxel as a treatment option in the control group, reflecting its status as a standard of care for mCRPC following progression on an ARPI (6). Notably, rucaparib was shown to outperform docetaxel in this context. In the BRCA group, rucaparib led to an improved PFS relative to docetaxel-treated patients in the control group (n=60). Specifically, the median PFS was 11.2 months (95% CI: 9.2–13.8) for the rucaparib arm versus 8.3 months (95% CI: 6.1–9.9) for the docetaxel-treated patients. This resulted in a HR of 0.53 (95% CI: 0.37–0.77). This benefit extended to the ITT population, with a median PFS of 10.2 months (95% CI: 8.3–11.2) in the rucaparib arm versus 8.3 months (95% CI: 6.1–10.1) for the docetaxel-treated patients (n=75; HR, 0.64; 95% CI: 0.46–0.88).

As expected from prior experience with PARPi in prostate and other cancer types, the most common grade ≥3 adverse events were anemia (24%; 64/270) and thrombocytopenia (6%; 16/270). Of note, there were an elevated proportion of patients experiencing rash (29%; 78/270) and increased liver function tests (LFTs) (27%; 72/270) in the rucaparib arm, with 5% (14/270) of patients experiencing grade 3 LFT elevation. These may represent rucaparib specific adverse events, as trials with other PARPi in mCRPC report an incidence of under 10% for rash or elevated LFTs (7-9). Only 15% (40/270) of patients in the rucaparib arm discontinued therapy due to adverse events, compared with 22% (28/130) in the control arm. There were no observed cases of myelodysplastic syndromes or acute myelogenous leukemia.

The TRITON3 study establishes the benefit of rucaparib in the second line setting for *BRCA*-mutated mCRPC. This builds upon the findings of the TRITON2 study, which assessed rucaparib in mCRPC following progression on a taxane-based chemotherapy (4). In addition, the PROfound trial, published in 2020, validated the use of olaparib as a second-line therapy in mCRPC with mutations in one of 14 homologous recombination repair (mHRR) genes (3). However, the PROfound study was constrained by its exclusion of docetaxel from the comparator arm. Taken together, these studies affirm the role of PARP inhibitors as a second-line therapeutic strategy for homologous repair-deficient mCRPC. As a result, this approach is now considered standard care and is recommended by clinical guidelines (6).

There remain several key questions about the use of PARPi in mCRPC. First, what is the role of PARPi in earlier stages of disease? The PROpel (10), TALAPRO-2 (8), and MAGNITUDE (9) trials begin to address this question by assessing PARPi + ARPI in the first line setting of mCRPC. The PROpel and MAGNITUDE studies tested the combinations of olaparib with abiraterone/prednisone, and niraparib with abiraterone/prednisone, respectively, versus a control group receiving abiraterone/prednisone in the first-line mCRPC setting. The TALAPRO-2 study compared the combination of enzalutamide with talazoparib to enzalutamide with placebo in a similar patient population. The outcomes of these trials have been recently discussed in detail elsewhere (11,12). Briefly, preliminary results from these studies indicated an improvement in PFS when compared to physician's choice in patients with mHRR. Based on these findings, the FDA has approved olaparib (13) and niraparib (14) in combination with abiraterone/prednisone for *BRCA1/2*-mutated mCRPC, and talazoparib (15) with enzalutamide for mHRR mCRPC (12-gene panel).

However, despite these advancements, significant questions remain unanswered. Crucially, OS data are still immature in many of these trials, and a definitive benefit in OS has yet to be established. Given the added toxicities associated with PARPi, the benefits of combining PARPi with ARPI need to be weighed against the potential adverse effects and compared to sequential therapy, which is the current standard-of-care approach (6). Furthermore, the PROpel/MAGNITUDE/TALAPRO-2 studies required that patients be treatment-naive to ARPIs in the metastatic castration sensitive prostate cancer (mCSPC) setting, a requirement that no longer aligns with the current standard of care (6). As such, these studies do not definitively answer the question of whether combination androgen receptor signaling inhibitor (ARSI) + PARPi is superior to each monotherapy used sequentially. In view of these limitations, the authors acknowledge that in the first-line mCRPC setting, both PARPi as a monotherapy or in conjunction with abiraterone or enzalutamide are reasonable options for patients with *BRCA1/2* alterations. Additionally, while the majority of patients on the PROpel/MAGNITUDE/TALAPRO-2 trials were not previously treated with an ARSI in the hormone-sensitive space, it may be reasonable in certain settings to use a combination of ARSI + PARP

Table 1 HRR related gene panels across phase III studies in mCRPC

Study	Disease setting	Agent	HRR genes	Method
TRITON3 (5)	2nd line	Rucaparib	*BRCA1, BRCA2, and ATM*	Variable[a]
PROfound (3)	2nd line	Olaparib	*BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, PPP2R2A*[b] *and RAD54L*	Panel-based DNA sequencing
MAGNITUDE (9)	1st line	Niraparib (plus abiraterone)	*ATM, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, HDAC2, and PALB2*[c]	Panel-based DNA sequencing
TALAPRO-2 (8)	1st line	Talazoparib (plus enzalutamide)	*BRCA1, BRCA2, PALB2, ATM, ATR, CHEK2, FANCA, RAD51C, NBN, MLH1, MRE11A, and CDK12*	Panel-based DNA sequencing
PROpel (10)	1st line	Olaparib (plus abiraterone)	*ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, and RAD54L*[c]	Panel-based DNA sequencing

[a], any approved institutional or commercial clinical-grade test for mutations in HRR (mHRR) status was allowed, including germline-only testing; [b], PPP2R2A was included in the HRR panel in the *PROfound* study but was ultimately removed from the FDA indication due to lack of efficacy; [c], the FDA has only approved niraparib and olaparib in combination with abiraterone for first-line treatment of mCRPC in patients with BRCA1/2 alterations. HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; FDA, Food and Drug Administration.

inhibitor in men previously treated with androgen deprivation therapy (ADT) + ARSI for metastatic hormone-sensitive prostate cancer (mHSPC). In these scenarios, the authors recommend alternating the ARSI agent. For example, in a patient with a BRCA2 mutation who was previously treated with ADT + abiraterone for mHSPC, it may be reasonable to use enzalutamide + talazoparib upon progression to mCRPC.

A second question that arises is the appropriate patient selection for therapy with PARPi. Trials assessing PARPi in the second-line setting, such as TRITON3 and PROfound, were conducted exclusively in patients with mHRR mCRPC, although the list of HRR genes varied between studies (*Table 1*). The TRITON3 study included patients with deleterious mutations in *BRCA1/2* or *ATM*. It allowed any commercial or institutional sequencing platform and accepted both tissue-based testing as well as circulating tumor DNA testing; a pathogenic germline-only mutation was also accepted. On the other hand, the PROfound study employed a companion diagnostic test to identify alterations in 15 HRR genes: *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*. Deleterious mutations were defined as either protein-truncating mutations or missense mutations categorized as deleterious. Despite differences in biomarker selection, the benefit was mostly limited to patients with *BRCA2* mutations in both studies. For instance, the TRITON3 study's exploratory subgroup analysis on patients with *ATM* mutations (representing about 25% of the ITT cohort) showed no improvement in PFS with rucaparib compared to the control group. Furthermore, no radiographic objective responses to rucaparib were noted in this subgroup. Similarly, gene-specific analysis of the PROfound study showed no improvement in PFS or OS among patients with *CDK12* (n=61 olaparib, n=24 control) or *ATM* (n=62 olaparib, n=24 control) mutations (7). However, it's worth noting that the gene-specific analysis of non-*BRCA2* HRR genes in the PROfound study was constrained by the small sample size.

These findings reinforce the notion that the greatest benefits from PARPi in mCRPC are seen in patients with *BRCA2* mutations. However, they do not rule out potential benefits for some patients with other HRR gene mutations. In fact, occasional responses among patients with non-*BRCA2* mutations are well documented (16-18). Furthermore, in the MAGNITUDE, TALAPRO-2, and PROpel studies, patients could be enrolled even without HRR mutations. While the results were conflicting, some improvement in PFS among non-mHRR groups treated with PARPi compared to the control group was observed in both the TALAPRO-2 and PROpel studies, but not in the MAGNITUDE trial. It's crucial to note that the definition of mHRR differed across all the studies (*Table 1*), and that the most consistent benefit was observed in mHRR groups,

especially those with *BRCA2* mutations.

Several factors could explain why mHRR status and mutations in specific HRR genes have yielded inconsistent treatment responses to PARPi in mCRPC. Firstly, the canonical mechanism of PARP inhibition exploits the synthetic lethal relationship between the loss of HRR function (such as through inactivation of *BRCA1* or *BRCA2*) and the pharmacological inhibition of compensatory DNA repair mechanisms, such as non-homologous end joining (NHEJ) (19). Homologous repair deficiency (HRD) and the subsequent reliance on NHEJ and other DNA damage repair pathways can create measurable "genomic scars", reflected by loss of heterozygosity, large-scale transitions, and telomeric allelic imbalance (20). These characteristics can collectively contribute to an "HRD score", providing insights into the functional dependence on non-HRD mechanisms of DNA repair. As one might expect, the bi-allelic inactivation of an HRR gene is more likely to be associated with the HRD phenotype. In prostate cancer, a correlation has been observed between bi-allelic vs mono-allelic loss of *BRCA2* and the degree of "HRD score" (20). However, in the clinical trials discussed above, biomarker testing was agnostic of bi-allelic inactivation of mHRR genes or the degree of "genomic scars". Therefore, the inclusion of functional HRD assays may enhance the specificity of mHRR testing by confirming that mutations in HRR genes result in a functional impact on the genome. Functional HRD assays could also potentially increase the sensitivity of mHRR testing, as there are cases of significant genomic instability in the absence of a detectable mutation in HRR (i.e., when HRR deficiency is due to epigenetic silencing or complex structural rearrangements) (20,21). Functional HRD tests are clinically used in other tumor types (specifically, ovarian cancer), but they remain experimental in prostate cancer (19,22). It is important to note that in an integrated molecular analysis of mCRPC, alterations in *BRCA2* were biallelic in up to 90% of cases, which could potentially explain why *BRCA2* mutation testing appears to be the most consistent marker of PARPi response in mCRPC (21). In support of this, mCRPC patients with homozygous *BRCA2* deletion demonstrate exceptional responses to PARPi (23,24). Biallelic inactivation of other HRR genes (*BRCA1*, *ATM*) is less frequent in prostate cancer (25,26), though when they occur are also typically associated with benefit to PARPi (24).

Another complicating factor is the potential for non-canonical mechanisms of actions for PARPi in prostate cancer. Preclinical evidence indicates that androgen receptor (AR) signaling activates certain HRR genes, and subsequent androgen deprivation may result in a state of HRD (27). This mechanism would theoretically be independent of any mutations in HRR genes and could potentially be clinically relevant. This may potentially explain the clinical outcomes observed in the HRR wild-type cohorts in the PROpel and TALAPRO-2 studies, though the results in non-mHRR cohorts are conflicting (8-10,12). However, it is equally plausible that the observed outcomes could be due to the low sensitivity of panel-based testing or the use of circulating tumor DNA (ctDNA) to detect mHRR. Another non-canonical mechanism is the potential for PARP-1 to regulate the transcription of the AR itself, though the clinical relevance of this pathway is still to be determined (28). These examples highlight the complexity of the action of PARPi and underline the need for a deeper understanding of their function and mechanisms. It is worth noting the CASPAR study (NCT04455750), a phase III trial of enzalutamide plus rucaparib or placebo as first line therapy in mCRPC, is enrolling patients in an HRR agnostic manner, and may help clarify the role of PARPi in the non-mHRR setting for prostate cancer.

In conclusion, the TRITON3 trial validates the advantage of rucaparib over both docetaxel and ARPI in second-line treatment for mCRPC patients with *BRCA1/2* mutations. But it fell short of achieving a trifecta, with no meaningful activity in the *ATM*-mutated group. Thus, it remains to be seen whether the FDA will expand the label of rucaparib to also include deleterious *ATM* alterations, or whether it will continue to restrict its use to those with *BRCA1/2* mutations. In our opinion, the broad use of rucaparib in *ATM*-altered mCRPC is not justified. Substantial work still needs to be done to optimize patient selection and establish the best timing for PARPi administration within the treatment paradigm, and additional discriminating biomarkers are needed both for better inclusion and exclusion of PARP inhibitor use in mCRPC.

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Footnote

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