Editorial Commentary

How far does a new horizon extend for rucaparib in metastatic prostate cancer?

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In the ongoing quest for precision medicine solutions to intricate oncologic challenges, Poly (ADP-ribose) polymerase (PARP) inhibitors (PARPi) have risen to prominence in metastatic prostate cancer in patients that harbor *BRCA* mutations with the Food and Drug Administration (FDA) approvals of olaparib and rucaparib. In the TRITON-3 clinical trial, Fizazi *et al.* presents the results of a randomized, open-label phase 3 study of patients with metastatic castrate-resistant prostate cancer (mCRPC) with a *BRCA1/2* or *ATM* mutations who had disease progression with a novel hormonal therapy (NHT) which included abiraterone, enzalutamide, apalutamide or an investigational agent (1). Taxane-based therapy or an NHT for castrate-sensitive disease was permitted. Patients were assigned in a 2:1 ratio to receive the oral PARP inhibitor, rucaparib at 600 mg by mouth twice daily, or physician's choice of docetaxel or NHT: abiraterone or enzalutamide. The primary outcome was radiographic progression-free survival (rPFS), according to an independent review. Of note, crossover to receive rucaparib was permitted after disease progression was confirmed by an independent review.

In this international trial, 405 patients had deleterious *BRCA* or *ATM* alterations, 270 underwent randomization to the rucaparib group, and 135 patients were randomized to the physician's choice group. The results show at 62 months, the median rPFS was longer in the rucaparib group compared to the physician's choice group in the *BRCA* subgroup, 11.2 *vs.* 6.4 months [hazard ratio (HR), 0.50; 95% confidence interval (CI): 0.36 to 0.69], and the intention-to-treat (ITT) population, 10.2 *vs.* 6.4 months (HR, 0.61; 95% CI: 0.47 to 0.80). While P<0.001 for both comparisons, in the *ATM* subgroup, the results were not as robust with median rPFS of 8.1 months (95% CI: 5.5 to 8.3) in the rucaparib group *vs.* 6.8 months in the control group (95% CI: 4.0 to 10.4). Secondary outcomes included median overall survival (OS), wherein the *BRCA* subgroup, OS was 24.3 months (95% CI: 19.9 to 25.7) *vs.* 20.8 months (95% CI: 16.3 to 23.1) in the control group (HR, 0.81; 95% CI: 0.58 to 1.12; P=0.21). Patient reported outcomes were assessed from baseline to week 25 on the Functional Assessment of Cancer Therapy-Prostate (FACT-P) Questionnaire. Interestingly, in the *BRCA* subgroup and the ITT population, changes in the score were similar for rucaparib and the control medications. The most common adverse events (AEs) reported for patients treated with olaparib were fatigue, nausea, and anemia, while in the control group, the most common AEs were fatigue, diarrhea, and neuropathy. For grade 3 and above, anemia, neutropenia, and fatigue were seen in the rucaparib group *vs.* fatigue and neutropenia in the control group. No myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) cases were reported with rucaparib treatment.

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In the setting of mCRPC, the success of an individualized approach to treatment has varied particularly dependent on genetics. In 2015, Robinson *et al.* conducted a prospective whole-exome and transcriptome sequencing of bone or soft tissue tumor biopsies from 150 patients with mCRPC (2). Alterations in *BRCA1/2* and *ATM* were identified at higher frequencies than anticipated, with analysis of somatic and pathogenic alterations in *BRCA2* in 19/150 cases (12.7%). From identifying alterations that were potentially actionable in the DNA damage repair (DDR) pathways, further research indicated the PARP inhibitor olaparib had anti-tumor activity in mCRPC in patients with aberrations in the DDR genes based on a composite endpoint with the highest number of responses again in the *BRCA1/2* subgroup (3). When selecting patients with mCRPC for treatment with PARPi, after treatment and progression on enzalutamide or abiraterone, data from the phase 3 PROfound study evaluating single-agent olaparib showed rPFS was longer in the olaparib group in patients with at least one alteration in *BRCA1/2* or *ATM vs.* physician's choice of enzalutamide or abiraterone (7.4 *vs.* 3.6 months; HR, 0.34; 95% CI: 0.25 to 0.47; P<0.001) (4). The median OS in the *BRCA1/2* and *ATM* cohort was 18.5 *vs.* 15.1 months in the control group. Based on these results, in May 2020, the FDA approved olaparib for patients with deleterious or suspected deleterious germline or somatic DDR mutations in mCRPC whose disease had progressed on enzalutamide or abiraterone (5).

TRITON-3 was the second phase 3 trial to evaluate a PARP inhibitor in mCRPC in patients harboring DDR mutations, but the first trial to compare any PARP inhibitor with docetaxel, a mainstay of treatment in metastatic disease (6,7). Not only was rucaparib granted accelerated approval previously by the FDA in May 2020 based on the results of the phase 2 TRITON-2 study (8), but in TRITON-3 when comparing rucaparib *vs.* physician's choice, which included docetaxel, the subgroup analyses of rPFS for standard therapies revealed patients harboring *BRCA1/2* mutations (*BRCAm*) in mCRPC had an rPFS benefit when compared to docetaxel (in addition to clear benefit when compared to enzalutamide or abiraterone). Of note, while the benefits were clearly outlined in *BRCAm* disease, but what was not seen was benefit in the *ATM*-mutated population. In the 270 patients treated with rucaparib, 64% harbored a *BRCA2* mutation, while only 26% harbored *ATM* mutations. The prevalence and mutational variations in the *ATM* gene need further investigations in clinical trials with both PARPi and other targeted therapies as this population does not display a robust benefit to treatment with single agent PARPi. Even smaller was *BRCA1* mutations at 11% of the total gene mutations in the rucaparib group.

After disease progression on enzalutamide, abiraterone, or apalutamide, men harboring *BRCA2* mutations should be offered rucaparib or olaparib as a treatment option prior to a second NHT or even docetaxel based on the results seen in TRITON-3. What remains are questions focused on greater nuances in how we treat patients with mCRPC. First, as with most clinical studies, access to the trial was limited, as seen in the demographic characteristics at baseline in the ITT population. In the study, a total of 14 patients identified as Black, 5 as Asian, and 73 patients were not identified (missing data). Genetic and genomic testing is increasingly important in identifying optimal clinical management (9), but how successful are clinicians in treatment strategies when we are missing a significant proportion of the population in testing and efficacy endpoints? The need to expand testing and eligibility criteria in order to access under-represented minorities (URMs) is vital (10). Another important aspect is to provide standardization to genetic genomic testing. In TRITON-3, plasma testing was the most consistent mode of testing with 63% in the rucaparib group and 59% in the control group. This was followed by tissue testing at 79% and 29%, respectively. Alterations were determined by central testing of tissue and/or plasma, next-generation sequencing, or local testing (11). To ensure adequate sequencing, of both blood and tissue, it will be important to identify adequate testing platforms, particularly as circulating tumor DNA (ctDNA) becomes more prevalent as a tool for liquid biopsies (12). In terms of practical applications, certified platforms for testing of both plasma and tissue needs to be consistent amongst participants and tools for liquid biopsies need to be validated. Integrating genetic testing will give insight into somatic and germline alterations and the relevance of specific genes in relation to outcomes with PARPi. Not all alterations are created equally, particularly in DDR pathways, and future analyses need to determine the drivers of response between genes, particularly when considering *BRCA2 vs. BRCA1* mutations. Are *BRCA2* mutations the key to personalized approaches with PARPi? Beyond the type of mutation itself, what are the implications of different types and locations of *BRCA* mutations (13) in mCRPC? As seen in breast and ovarian cancers, types and locations of *BRCAm* differ leading to differing survival based on genetics. While *ATM* alterations are often grouped with *BRCAm*, TRITON-3 did show, despite small numbers, rucaparib did not extend

survival in this group of patients.

While single-agent rucaparib and olaparib were validated in *BRCAm* mCRPC, combination strategies with NHTs have been published or presented, but in patients regardless of mutational status. In the randomized phase 3, TALAPRO-2 study, the PARPi talazoparib was combined with enzalutamide *vs.* single agent enzalutamide as first-line treatment in biomarker unselected mCRPC with a primary endpoint of rPFS (14). Median rPFS was not reached in the in the talazoparib group (95% CI: 27.5 months–not reached) and 21.9 months (95% CI: 16.6–25.1) for the placebo group. Patients with *BRCA2m* benefitted most from the combination treatment (HR, 0.20; 95% CI: 0.11–0.36, P<0.0001). Patients were prospectively assessed for DDR mutations, and OS survival data is pending to determine the benefit of the combination treatment based on mutational status. The combination arm's toxicity profile revealed more dose interruptions and dose reductions and grade 3 or greater anemia. Long-term data on toxicities, particularly of MDS or AML, is needed. As such, long-term follow-up at regular intervals is needed on the participants enrolled on TRITON-3 to determine rates of toxicities, including MDS and AML. Similarly, PROpel, the double-blind, phase 3 trial of abiraterone plus olaparib *vs.* abiraterone plus placebo in patients with mCRPC, biomarker unselected, showed a median imaging-based PFS benefit in the abiraterone plus olaparib arm *vs.* the abiraterone plus placebo arm (24.8 *vs.* 16.6 months; HR, 0.66; 95% CI: 0.54 to 0.81; P<0.001) (15). Retrospective analysis of tissue and ctDNA were performed to determine mutational status. Again, the toxicity profile was notable for AEs, including pulmonary embolism (6.5%) in the abiraterone plus olaparib arm *vs.* 1.8% in the placebo arm. There was no crossover in this study; thus, the question of sequential *vs.* combination treatments remains unknown. Additionally, the PARPi niraparib plus abiraterone combination has been FDA-approved in *BRCA1/2m* mCRPC based on an rPFS benefit seen in the phase 3 MAGNITUDE trial (16). While the trend for intensification in treatment strategies in metastatic prostate cancer continues, questions regarding this approach remain and clinical trials with sequential designs would help to elucidate how and when treatments should be sequenced, or if of greater benefit with manageable toxicities, combined. Consideration should be given to other possible combination strategies with PARPi with further translational data, including angiogenesis inhibitors.

TRITON-3 effectively showed single agent rucaparib has rPFS benefit in patients with *BRCA2* mutations in mCRPC and led to the first accelerated FDA approval of a PARPi a biomarker-selected cohort in mCRPC. What is evident is greater access to genetic testing, and genetic counseling is needed for patients with metastatic disease, which will give more insight into the type and locations of mutations involved with DDR and other potentially targetable pathways. Genetic counseling needs to be made standard for all patients with metastatic prostate cancer with access being a main issue for many patients. In the future, clinical trials need to expand eligibility criteria to ensure a broader and more representative participant population is enrolled onto trials as this significantly impacts outcome measures being assessed. It is widely known genetic testing and counseling in URMs needs concentrated efforts for accessibility and implementation. Committing to partnerships with community medical teams who serve URMs and aiming to implement diversity strategies in clinical trial design are ways in which to begin to delve into this important, and often overlooked, issue. Additionally, long-term follow up for safety and tolerability needs to be incorporated into such clinical trials. Consideration is also needed for addressing resistance mechanisms to single agent PARPi and sequencing of PARPi after resistance and progression with other PARPi and with NHTs. Clearly, what lies ahead is a personalized, biomarker-driven approach in mCRPC and a greater understanding of the selection and identification of patients who will benefit the most from this approach.

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