Editorial Commentary

The growing role of PARP inhibitors in the treatment of metastatic castration-resistant prostate cancer

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Comment on: Fizazi K, Piulats JM, Reaume MN, *et al.* Rucaparib or Physician's Choice in Metastatic Prostate Cancer. N Engl J Med 2023;388:719-32.

Keywords: Prostate cancer; poly (ADP-ribose) polymerase inhibitors (PARPis); castration-resistant; germline mutations

Submitted Aug 21, 2023. Accepted for publication Oct 20, 2023. Published online Nov 13, 2023.

doi: 10.21037/tcr-23-1515

View this article at: https://dx.doi.org/10.21037/tcr-23-1515

Introduction

Androgen deprivation therapy (ADT) is a cornerstone of medical treatment for metastatic prostate cancer (1). However, progression to metastatic castration-resistant prostate cancer (mCRPC) is eventually inevitable (2). Determining appropriate management of patients with mCRPC is difficult and compounded by a high prevalence of germline mutations among this population. Pritchard *et al.* [2016] have shown that 11.8% of advanced metastatic prostate cancer patients harbor germline aberrations in genes responsible for maintaining DNA integrity, with *BRCA2* mutations consisting of 44% of these mutations (3). Recent investigations into numerous poly(ADP-ribose) polymerase (PARP) inhibitors (PARPis) have shown promising results for effective management of patients with known germline mutations, especially *BRCA1* and *BRCA2* (4). These studies include the PROfound (olaparib, phase 3) (5) GALAHAD (niraparib, phase 2) (6), and TALAPRO-1 (talazoparib, phase 2) (7) clinical trials. Most recently, the TRITON3 phase 3 clinical trial published results investigating the efficacy and adverse effects of the PARPi rucaparib compared to physicians' choice standard of care (PCSC) (8). The PCSC included either docetaxel or a second-generation androgen-receptor pathway inhibitor (ARPI) in the setting of mCRPC patients with either *BRCA1*, *BRCA2*, or *ATM* gene mutations (8). In this editorial, we aim to summarize the most significant findings of the TRITON3 trial and compare these to other similar trials (GALAHAD, TALAPRO-1, and PROfound).

PARPi activity and resistance

Mechanism of action

PARPs are enzymes which control the ADP-ribosylation process, an important post-translational modification controlling various cellular processes such DNA repair, transcription, and apoptosis. Eighteen distinct PARPs exist in humans, of which *PARP1*, *PARP2*, and *PARP3* are involved in DNA damage response and repair. *PARP1* is the most abundant regarding DNA repair and the most prevalent to the mechanism of PARPi efficacy (9).

Defects in the ADP-ribosylation process cause genomic instability. Therefore, the inactivation of PARPs in cancer patients with germline mutations, such as *BRCA1* and *BRCA2*, is a key treatment modality being explored. Tumors with *BRCA1/2* loss of function appear more sensitive to PARPi, as inhibiting PARP activity causes an increase in double strand breaks and replication fork collapse at a higher rate within tumor cells for these patients (9).

PARPi interrupts the ADP-ribosylation process of *PARP1* through binding to the protein's catalytic domain. This adherence prevents auto-modification, as well as traps *PARP1* within chromatin. This impairment prevents auto-modification directed release from DNA during repair and

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contributes to cell lethality (9).

All PARPi share the ability to bind to the catalytic binding domain of *PARP1*. However, evidence suggests that the strength of trapping varies based on the PARPi. This difference may be related to variations in molecular shape and flexibility (10). Additionally, certain PARPi demonstrate an allosteric effect at a region on the *PARP1* molecule known as the helical domain. This allosteric activity augments the effect of PARPi on *PARP1* affinity modification and retention at the DNA break. Previous literature has categorized PARPi into three general categories based on the allosteric effect of the drug on *PARP1* affinity. Type 1 or "pro-retention" PARPi display a strong allosteric effect which destabilizes the helical domain. Type 2 "non-allosteric" PARPi, such as olaparib and talazoparib are relatively neutral allosterically and primarily exert their effect through catalytic inhibition of *PARP1* allosteric release. Finally, type 3 "pro-release" PARPi, including veliparib, niraparib, and rucaparib, stabilize the helical domain, reducing *PARP1* affinity and promoting its release (10).

Resistance to PARPis

A number of mechanisms of resistance to PARPi have been proposed in recent literature. The genomic instability caused by PARPi has the potential to disrupt multiple genes leading to reversion mutations in which the original DNA reading frame is restored. Restoration of the reading frame sustains activity of *BRCA1/2* and the homologous recombination repair (HRR) mechanism and reduces the efficacy of PARPi (11). Reversion mutations are suspected as the most common mechanism of PARPi resistance. Within the TRITON2 clinical trial of rucaparib, 39 of 100 patients were found to possess *BRCA* revision mutations (12).

Mutations which affect promoter sequences have also been shown to confer resistance to PARPi activity. In the case of triple-negative breast cancer, hypermethylation of the promoter sequence has been showed to promote genetic silencing. Processes which promote demethylation enable residual transcription and reduce the efficacy of PARPi. Similarly, heterogenous promoter activity due to chromosomal rearrangement has shown the potential to similarly promote residual transcription and confer PARPi resistance despite an active, hypermethylated promoter region (11).

Summary of TRITON3 results in comparison to similar clinical trials

TRITON3 (rucaparib)

The TRITON3 trial is a randomized, controlled phase 3 clinical trial which included 405 patients with mCRPC and either *BRCA1*, *BRCA2*, or *ATM* gene mutations. Two hundred and seventy patients were randomized to receive oral rucaparib (600 mg twice daily), while 135 were assigned to receive PCSC regimens including either docetaxel or a second-generation ARPI (8) (*Table 1*). The primary endpoint was progression-free survival (PFS) determined by prespecified criteria on independent review, while secondary endpoints included overall survival (OS) and confirmed objective response rate (ORR).

Patients receiving rucaparib demonstrated significantly longer PFS compared to those receiving PCSC [median 10.2 and 6.4 months, respectively; hazard ratio (HR) =0.61; 95% confidence interval (CI): 0.47 to 0.80; P<0.001] (*Table 2*). Subgroup analysis of patients with *BRCA* mutations demonstrated an even greater difference in favor of rucaparib, with median durations of 11.2 and 6.4 months, respectively (HR =0.50; 95% CI: 0.36 to 0.69; P<0.001). In contrast, no significant difference was found when assessing the patients with *ATM* gene mutations (8.1 *vs.* 6.8 months, respectively; HR =0.95; 95% CI: 0.59 to 1.52). The median OS was compared between rucaparib and PCSC within the *BRCA* subgroup. This analysis of immature study data showed no significant difference between the two treatment regimens, with a median of 24.3 and 20.8 months, respectively (HR =0.81; 95% CI: 0.58 to 1.12; P=0.21). Furthermore, confirmed ORR for rucaparib and PCSC was found to be 45% and 17% in the *BRCA* subgroup, 35% and 16% in the intention to treat population, and 0% and 14% in the *ATM* subgroup, respectively.

PROfound trial (olaparib)

Similar to the TRITON3 trial, the PROfound trial, published in 2020, is a phase 3 clinical trial investigating the efficacy of the PARPi olaparib among patients with mCRPC and homologous recombination gene mutations who previously progressed while taking new hormonal agents (either enzalutamide or abiraterone) (5). Patients with either *BRCA1*, *BRCA2*, or *ATM* gene mutations were stratified into cohort A (n=245), while patients with mutations in any

Table 1 Demographic and baseline clinical data on patients included in the TRITON3, PROfound, and GALHAD trials

Parameters	Rucaparib (TRITON3 phase 3 trial)	Olaparib (PROfound phase 3 trial)	Niraparib (GALAHAD phase 2 trial)	Talazoparib (TALAPRO-1 phase 2 trial)
Number of men	405	387	289	127
Age (years), median [range]	Rucaparib group: 70 [45–90]	Olaparib group: 69 [47–91]	*BRCA* cohort:67 [63–73]	*BRCA* cohort: 69.0 [63.0–67.0]
	Control group: 71 [47–92]	Control group: 69 [49–87]	Non-*BRCA* cohort: 70 [66–75]	Overall: 69.0 [63.0–73.0]
Disease state	mCRPC	mCRPC	mCRPC	mCRPC
ECOG performance status, n [%]				
0	132 [49] (rucaparib)/68 [50] (control)	131 [51] (olaparib)/55 [41] (control)	48 [41] (*BRCA*)/18 [22] (non-*BRCA*)	24 [39] (*BRCA*)/52 [41 (overall)
1	138 [51] (rucaparib)/67 [50] (control)	112 [44] (olaparib)/71 [54] (control)	78 [55] (*BRCA*)/47 [58] (non-*BRCA*)	31 [51] (*BRCA*)/63 [50] (overall)
2	–	13 [5] (olaparib)/4 [3] (control)	16 [11] (*BRCA*)/11 [23] (non-*BRCA*)	6 [10] (*BRCA*)/12 [9] (overall)
Gleason score ≥8 at diagnosis, n [%]	Rucaparib: 173 [64]	Olaparib: 183 [73]	*BRCA* cohort: 96 [71]	*BRCA* cohort: 39 [64]
	Control: 96 [71]	Control: 95 [75]	Non-*BRCA* cohort: 51 [66]	Overall: 78 [61]
Genetic mutations	*BRCA*, *ATM*	*BRCA1*, *BRCA2*, *ATM*, *BRIP1*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, *RAD54L*	*ATM*, *BRCA1*, *BRCA2*, *BRIP1*, *CHEK2*, *FANCA*, *HDAC2*, *PALB2*	*ATM*, *ATR*, *BRCA1*, *BRCA2*, *CHEK2*, *FANCA*, *MLH1*, *MRE11A*, *NBN*, *PALB2*, *RAD51C*
Prior therapy	Second-generation ARPI (abiraterone acetate, enzalutamide, apalutamide, or an investigational agent) without chemotherapy for castration-resistant disease	enzalutamide or abiraterone for castration-resistant prostate cancer or for metastatic hormone-sensitive prostate cancer	androgen signaling inhibitor and taxane chemotherapy (docetaxel, cabazitaxel, or both)	One or two taxane-based chemotherapy regimens (docetaxel or docetaxel and cabazitaxel) and enzalutamide, abiraterone, or both

ECOG, Eastern Cooperative Oncology Group; mCRPC, metastatic castration-resistant prostate cancer; ARPI, androgen-receptor pathway inhibitor.

Table 2 Comparison of rucaparib and olaparib results from respective trials

Results	TRITON3 trial			PROfound trial		
	Rucaparib	PCSC	P value	Olaparib	PCSC	P value
PFS in overall population (months), median	10.2	6.4	<0.001	5.8	3.5	<0.001
PFS *BRCA*1/*BRCA*2 (TRITON3) or *BRCA1*/*BRCA2*/*ATM* (PROfound) (months), median	11.2	6.4	<0.001	7.4	3.6	<0.001
Confirmed ORR (overall population) (%)	35	16	–	22	4	–
Confirmed ORR (germline cohort) (%)	45	17	–	33	2	<0.001
OS (months)	24.3	20.8	0.21	17.5	14.3	–

PCSC, physician choice standard of care; PFS, progression-free survival; ORR, objective response rate; OS, overall survival.

of 12 other prespecified genes were assigned as cohort B (n=142). Patients were randomized (2:1) to receive either olaparib or physician's choice of either enzalutamide or abiraterone.

As in the TRITON3 trial, PFS was assessed as the primary endpoint. Among the overall population, the authors report a significantly longer PFS duration for patients assigned to olaparib compared to those assigned to PCSC (median 5.8 *vs.* 3.5 months, respectively; HR =0.49; 95% CI: 0.38 to 0.63; P<0.001). When assessing the subgroup including exclusively patients with *BRCA1*, *BRCA2*, or *ATM* mutations, the difference was even greater in favor of the PARPi. Among this population, olaparib demonstrated a median PFS of 7.4 months compared to just 3.6 months for the control group (HR for progression or death =0.34; 95% CI: 0.25 to 0.4; P<0.001).

Additional endpoints of the PROfound trial included confirmed ORR, median time to pain progression, and OS. Among cohort A, a substantially higher response rate was observed in patients on olaparib (33%) compared to those in the control treatment group (2%) (odds ratio for an objective response =20.86; 95% CI: 4.18 to 379.18; P<0.001). Patients within this cohort taking olaparib also displayed a significantly longer median time to pain progression, with 84% of olaparib patients reaching the 6-month mark without pain progression compared to 64% of control group patients (HR =0.44; 95% CI: 0.22 to 0.91; P=0.02). Cohort A patients on olaparib also attained significantly longer OS, with a median of 18.5 months compared to 15.1 months for the control group (HR for death =0.64; 95% CI: 0.43 to 0.97; P=0.02). Consistent results were found when assessing these endpoints for the overall population, with olaparib patients demonstrating higher confirmed response rate (22% *vs.* 4%; odds ratio =5.93; 95% CI: 2.01 to 25.40), higher rate of patients without pain progression after 6 months (85% *vs.* 75%) and higher OS at 41% data maturity (17.5 *vs.* 14.3 months; HR for death =0.67; 95% CI: 0.49 to 0.93). A comparison of the results from the TRITON3 and PROfound trials is displayed in *Table 2*.

GALAHAD trial (niraparib)

The GALAHAD trial is a phase 2 clinical trial published in 2022 enrolling 289 patients with mCRPC and DNA repair gene defects, who previously progressed on next-generation androgen signal inhibitors and taxanes (6). Patients received 200 mg of niraparib orally once daily throughout the trial. ORR was used as the primary endpoint to evaluate the efficacy of niraparib. Adverse effects were also monitored and recorded throughout the study.

Among patients with measurable disease in the *BRCA* cohort, 16 of 76 patients (21%) demonstrated confirmed response at a median follow-up of 10 months (95% CI: 23.7 to 46.0). Among the secondary endpoints investigated, the trial reports that 37/76 of the *BRCA* patients (49%) demonstrated a 30% decreased in the sum of the longest target lesion diameter compared to baseline. Additionally, the PFS rate of the total population was 61% at a median duration of 5.55 months (95% CI: 3.91 to 7.20) and the OS rate was 62%.

TALAPRO-1 trial (talazoparib)

Similar to the GALAHD trial, TALAPRO-1 is a phase 2 trial investigating the efficacy of talazoparib monotherapy among patients mCRPC. Eligibility criteria included age of 18 years or older, DNA repair mutations reported

Table 3 Adverse effects of rucaparib (TRITON3 phase 3) *vs.* olaparib (PROfound phase 3) *vs.* niraparib (GALHAD phase 2) *vs.* talazoparib (TALAPRO-1, phase 2)

Adverse effects	Rucaparib (TRITON3 phase 3 trial; n=270)	Olaparib (PROfound phase 3 trial; n=256)	Niraparib (GALAHAD phase 2 trial; n=289)	Talazoparib (TALAPRO-1 phase 2 trial; n=127)		
				Grade 1–2	Grade 3	Grade 4
Any adverse event	270 [100]	144 [95]	288 [100]		121 [95]	
Grade 3+ adverse event	161 [60]	130 [51]	217 [75]	50 [39]	57 [45]	4 [3]
Fatigue	165 [61]	105 [41]	106 [37]	12 [18]	2 [2]	0
Decreased appetite	96 [36]	77 [30]	93 [32]	32 [25]	4 [3]	0
Nausea	134 [50]	106 [41]	169 [58]	39 [31]	2 [2]	0
Vomiting	65 [24]	47 [18]	111 [38]	15 [12]	2 [2]	0
Diarrhea	83 [31]	54 [21]	–	21 [17]	0	0
Constipation	74 [27]	45 [18]	100 [35]	22 [17]	1 [1]	0
Back pain	60 [22]	35 [14]	64 [22]	16 [13]	1 [1]	0
Arthralgia	49 [18]	24 [9]	44 [15]	9 [7]	1 [1]	0
Peripheral edema	54 [20]	32 [12]	–	20 [16]	1 [1]	0
Dyspnea	44 [16]	26 [10]	–	15 [12]	2 [2]	0
Anemia/decreased hemoglobin	126 [47]	119 [46]	156 [55]	23 [18]	39 [31]	0
Rash	78 [29]	–	–	–	–	–
Increased creatinine	51 [19]	–	–	–	–	–
Thrombocytopenia	50 [19]	–	99 [34]	13 [10]	7 [6]	4 [3]
Neutropenia	37 [14]	–	44 [15]	11 [9]	10 [8]	0
Pulmonary embolism	9 [3]	11 [4]	–	1 [1]	6 [5]	0

Data are presented as n [%].

as sensitive to PARPi, as well as prior progression on enzalutamide, abiraterone, or both. The study enrolled 128 participants to receive oral talazoparib (1 mg per day, 0.75 mg per day among patients with renal impairment), 104 of which possessed measurable soft tissue disease (antitumor activity population). The primary endpoint of the trial was confirmed ORR. Safety and side effects of patients who received at least one dose of talazoparib were also monitored.

At a median of 16.4 months follow-up, an ORR of 29.8% (31 of 104 patients; 95% CI: 21.2 to 39.6) was observed. An objective response was confirmed in 26 of 57 (46%) patients with *BRCA2* mutations and 2 of 4 (50%) of patients with *BRCA1* mutations. Additionally, 67 of 84 (80%) patients with measurable disease and pre- and post-treatment assessments demonstrated a reduction in tumor burden while 69 of 84 (82%) showed reductions in prostate-specific antigen levels. These percentages were even higher among patients with *BRCA1* or *BRCA2* mutations, at 90% (47 of 52) and 85% (50 of 59), respectively.

Adverse effects

The reported adverse effects of rucaparib during the TRTON3 trial are summarized in *Table 3*. The most common adverse effects experienced by patients taking rucaparib included fatigue (61%), nausea (50%), and anemia (47%). A total of 60% of patients experienced grade 3 or higher adverse effects while taking rucaparib, the most common of which was anemia (24%). Notably, a sizable percentage of patients experienced hematologic disturbances in the form of thrombocytopenia (19%) and

neutropenia (14%).

Adverse effects from the PROfound phase 3 trial of olaparib, the GALAHAD phase 2 trial of niraparib, and the TALAPRO-1 phase 2 trial of talazoparib are also included in *Table 3* for comparison. All three trials reported similar, nearly universally present rates of adverse events which primarily consisted of fatigue, nausea, and anemia. Niraparib demonstrated the highest rate of grade 3 or higher adverse events at 75% of patients, compared to 60% and 51% for rucaparib and olaparib, respectively.

PARPi combination therapy trials

In addition to the aforementioned PARPi monotherapy trials, numerous recent phase 3 trials have investigated the use of PARPi in conjunction with additional therapies for mCRPC patients. These include the PROpel (13), MAGNITUDE (14), and TALAPRO-2 (15) trials. These trials compared the combination of olaparib and abiraterone plus prednisone, niraparib and abiraterone plus prednisone, and talazoparib and enzalutamide, respectively, to the same regimens with placebos in place of olaparib, niraparib, and talazoparib. All three trials included men with mCRPC and included sub-stratification for patients with HRR gene mutations. A recent systematic review assessed the results of these three trials and found that the combination of PARPi and androgen receptor axis-targeted agent (ARAT) significantly improved PFS among the overall population (35% improvement, P<0.01) and especially the *BRCA1/2* (68% improvement, P<0.01) and HRR mutated (45% improvement, P<0.001) cohorts (16). The PARPi group also demonstrated a 16% improvement in OS of the total population (HR =0.84; 95% CI: 0.72 to 0.98; P=0.02) and a 24% improvement among patients with HRR mutations (HR =0.76; 95% CI: 0.61 to 0.95). Patients within the *BRCA1/2* population demonstrated the greatest magnitude of improvement at 47%, but inconsistent results with a 95% CI of 0.18 to 1.56. Notably, a substantially higher prevalence of adverse events and grade 3 or higher anemia was reported for the PARPi/ARAT group (55.2% and 31.9%, respectively) compared to the placebo/ARAT group (17.9% and 4.9%), respectively. Trials assessing the combination of ARAT and PARPi compared to PARPi monotherapy are currently unavailable.

Notably, the PROpel trial reported a higher prevalence of pulmonary embolism events for patients in the PARPi arm of the study compared to those in the placebo group. The study reports 26 cases (6.5%) of pulmonary embolism in the olaparib and abiraterone group, one of which was fatal, compared to only 7 cases (1.8%) in the abiraterone and placebo group (13). The TALAPRO-2 trial also reported a higher rate of pulmonary embolism among the PARPi group compared to the placebo, affecting 10 (3%) patients within the talazoparib group compared to 3 (<1%) patients within the placebo group. It is unclear whether this increased prevalence is attributable to PARPi or is simply happenstance given the outstanding risk of pulmonary embolism among patients with prostate cancer (15).

Conclusions

The TRITON3 phase 3 clinical trial shows promising results for rucaparib as an effective treatment option for patients with mCRPC, especially those with *BRCA* gene mutations. The results seemed to be superior to current standard of care treatments of docetaxel and second-generation ARPI. The TRITON3 results are consistent with those from other similar trials, including the PROfound phase 3 trial investigating olaparib, showing improved PFS compared to physicians' choice of standard of care. The efficacy of PARPis across these trials appears to be greater in patients with *BRCA1* and *BRCA2* mutations compared to those with other forms of DNA repair defects. While adverse effects are nearly omnipresent, rucaparib appears generally tolerable with a similar side effect profile to other PARPis. Still, patients taking rucaparib require routine monitoring. In May of 2023, the U.S. Food and Drug Administration approved the use of olaparib and abiraterone with prednisone or prednisolone for the treatment of mCRPC in patients with *BRCA* related gene mutations (17). Since then, talazoparib and enzalutamide (18), as well as and niraparib and abiraterone acetate with prednisone (19), have also been approved for treating mCRPC in patients with HRR defects and *BRCA* mutations, respectively. It is not clear yet if PARPis, given either as monotherapy or as part of a combination with other drugs, will be approved for patients without HRR gene mutations.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned

by the editorial office, *Translational Cancer Research*. The article has undergone external peer review.

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1515/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1515/coif). H.G. reports personal payment as a Pfizer speaker and Bayer speaker, and personal payment for Myovant and Bayer advisory board. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Panzone J, Rood GJ, Goldberg H. The growing role of PARP inhibitors in the treatment of metastatic castration-resistant prostate cancer. Transl Cancer Res 2023;12(12):3233-3240. doi: 10.21037/tcr-23-1515

