

BRCA1 Versus BRCA2 and PARP Inhibitor Sensitivity in Prostate Cancer: More Different Than Alike?

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On May 15, 2020, prostate cancer entered the precision oncology era with accelerated approval from the US Food and Drug Administration (FDA) for the poly(ADP)-ribose polymerase (PARP) inhibitor rucaparib for treating patients with metastatic castration-resistant prostate cancer (mCRPC) who had deleterious germline or somatic *BRCA1* or *BRCA2* mutations and who had previously received an androgen receptor (AR)-directed therapy and a taxane-based chemotherapy. Four days later, on May 19, 2020, the FDA approved a second PARP inhibitor, olaparib, for treating patients with mCRPC who have a deleterious germline or somatic mutation in at least one of 14 homologous recombination repair (HRR) genes (*BRCA1* and *BRCA2* plus 12 other HRR genes: *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, or *RAD54L*) who had previously received an AR-directed therapy. The FDA's approval of olaparib in prostate cancer was based on a positive randomized phase III trial (PROfound; ClinicalTrials.gov identifier: [NCT02987543](https://clinicaltrials.gov/ct2/show/study/NCT02987543)) that showed an improvement in radiographic progression-free survival (rPFS) in patients with HRR-mutated mCRPC who received olaparib compared with abiraterone or enzalutamide.¹ In contrast, the accelerated FDA approval of rucaparib in prostate cancer was based on an uncontrolled single-arm phase II trial (TRITON2; ClinicalTrials.gov identifier: [NCT02952534](https://clinicaltrials.gov/ct2/show/study/NCT02952534)) that used objective response rate (ORR) as its primary efficacy end point, as presented in this issue in an article by Abida et al.² This accelerated regulatory approval, an unprecedented move by the FDA in the prostate cancer space, is contingent upon the confirmation of a clinical benefit with rucaparib in the ongoing randomized phase III trial (TRITON3; ClinicalTrials.gov identifier: [NCT02975934](https://clinicaltrials.gov/ct2/show/study/NCT02975934)), which is testing rucaparib versus physician's choice of best systemic therapy (AR-directed therapy or taxane chemotherapy) in taxane-naïve patients with mCRPC.

As reported in Abida et al,² the accompanying article, the TRITON2 study enrolled patients with mCRPC who had previously progressed on one to two lines of AR-directed therapy (eg, abiraterone or enzalutamide) and one line of taxane-based chemotherapy (eg, docetaxel) and who had a deleterious germline or somatic mutation in *BRCA1/2* or another non-*BRCA1/2* HRR

gene. Patients were treated with open-label rucaparib 600 mg orally twice per day (together with ongoing medical or surgical castration), until disease progression or unmanageable toxicity. Efficacy end points were the ORR in those with measurable soft tissue metastases, a 50% or greater decrease in prostate-specific antigen (PSA₅₀) level response rate, and rPFS. The activity of rucaparib in patients with mCRPC who had non-*BRCA1/2* HRR gene mutations has been reported previously³ and was not sufficient to warrant regulatory approval for that molecular subset of patients. In the cohort of 115 patients with *BRCA1* (13 patients) or *BRCA2* mutations (102 patients), the ORR for rucaparib was 44% (27 of 62 evaluable patients), the PSA₅₀ response rate was 55% (63 of 115 evaluable patients), and the median rPFS was 9.0 months (95% CI, 8.3 to 13.5 months), representing an impressive constellation of therapeutic benefits. It should also be noted that TRITON2 enrolled more patients with mCRPC who had *BRCA1* and *BRCA2* alterations than any other study of PARP inhibitors (including the PROfound study), an impressive feat. The safety profile of rucaparib was generally favorable but was notable for a prevalence of the following adverse events at grade 3 or greater: anemia (25%), thrombocytopenia (10%), asthenia or fatigue (9%), increases in hepatic transaminases (5%), and nausea (3%).

As an exploratory hypothesis-generating exercise, the authors examined the activity of rucaparib according to gene mutation (*BRCA1* or *BRCA2*), genetic origin (germline or somatic), zygosity status (monoallelic or biallelic), and mutation type (homozygous deletion or other deleterious mutations). This is the first study to explore the clinical significance of these genomic variables in prostate cancer, so the authors should be congratulated for shedding additional light on and providing new biologic insights into the activity of PARP inhibitors in prostate cancer. Accordingly, the efficacy of rucaparib was generally greater (although not always statistically superior) in patients with germline versus somatic *BRCA1/2* mutations (PSA₅₀ response, 61% v 51%, with similar ORR estimates), in patients with biallelic versus monoallelic mutations (PSA₅₀ response, 75% v 11%; ORR, 52% v 50%), and in patients with homozygous deletions versus other

ASSOCIATED CONTENT

See accompanying article on page 3763

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TABLE 1. Summary of Efficacy Data for a Range of PARP Inhibitors in Patients With mCRPC Comparing Outcomes in Those With Deleterious *BRCA1* Versus *BRCA2* Mutations

Outcome	TOPARP-A ¹⁴				PROfound ¹				TRITON2 ²				TALAPRO-116				Pooled Data			
	<i>BRCA1</i>		<i>BRCA2</i>		<i>BRCA1</i>		<i>BRCA2</i>		<i>BRCA1</i>		<i>BRCA2</i>		<i>BRCA1</i>		<i>BRCA2</i>		<i>BRCA1</i>	<i>BRCA2</i>		
	n/N	n/N	n/N (95% CI)	n/N (95% CI)	n/N	n/N (95% CI)	n/N (95% CI)	n/N (95% CI)	n/N	n/N (95% CI)	n/N (95% CI)	n/N (95% CI)	n/N	n/N (95% CI)	n/N (%)	n/N (%) (95% CI)				
PSA ₅₀	0/1	7/7	1/2	22/28	NR	NR	NR	NR	2/13	2/13	61/102	61/102	2/5	2/5	26/41	26/41	5/21 (23.8)	5/21 (23.8)	4.4 to 43.2	116/178 (65.2 to 72.2)
ORR	NE	5/5	0/1	11/20	0/5	24/43	24/43	3/9	3/9	24/53	24/53	2/4	2/4	15/37	15/37	5/19 (26.3)	5/19 (26.3)	5.1 to 47.5	79/158 (50.0 to 42.2 to 57.8)	
rPFS, months	NE	NR	NE	8.2 (5.5 to 13.0)	2.1 (1.4 to 5.5)	10.8 (9.2 to 13.1)	10.8 (9.2 to 13.1)	8.7 (1.8 to 10.7)	8.7 (1.8 to 10.7)	9.7 (8.3 to 14.0)	9.7 (8.3 to 14.0)	NR	NR	8.8 (5.6 to 19.2)	8.8 (5.6 to 19.2)	4.1 (1.0 to 16.8)	4.1 (1.0 to 16.8)	10.1 (8.9 to 11.6)	10.1 (8.9 to 11.6)	
No. of patients evaluable for rPFS				30	8	81	81	13	13	102	102	41	41	21	21	254	254			

NOTE. n/N denotes the number of patients who achieved a given end point out of the total number of evaluable patients for that end point.

Abbreviations: NE, not evaluable; NR, not reported; ORR, objective response rate; PSA₅₀, confirmed 50% or greater PSA response rate; rPFS, radiographic progression-free survival.

deleterious mutations (PSA₅₀ response, 81% v 49%; ORR, 60% v 38%). However, what is perhaps most interesting is the potential difference in efficacy of rucaparib in men with *BRCA1* compared with *BRCA2* mutations. More specifically, the clinical activity of rucaparib seemed to be generally greater in patients with *BRCA2*-altered compared with *BRCA1*-altered mCRPC, as assessed by PSA₅₀ response rates (60% [95% CI, 50% to 69%] v 15% [95% CI, 2% to 45%]), ORR estimates (45% [95% CI, 32% to 60%] v 33% [95% CI, 8% to 70%]), and median rPFS estimates (9.7 months [95% CI, 8.3 to 14.0 months] v 8.7 months [95% CI, 1.8 to 10.7 months]). Moreover, this apparent discrepancy in PARP inhibitor sensitivity between patients with *BRCA1*- and *BRCA2*-mutated mCRPC does not seem to be restricted to rucaparib and seems to be a class effect of PARP inhibitors in prostate cancer, as summarized in Table 1.

What could explain this dampened clinical activity of PARP inhibitors in patients with prostate cancer who have *BRCA1* compared with *BRCA2* mutations? We propose four hypotheses: (1) *BRCA1* alterations are less often germline lesions than *BRCA2* alterations, (2) *BRCA1* alterations are less often biallelic mutations than *BRCA2* alterations, (3) *BRCA1* mutations result in attenuated HRR deficiency compared with *BRCA2* mutations, and (4) *BRCA1* mutations have more genomic co-alterations (eg, in *TP53* or *PTEN*) than *BRCA2* mutations. We will examine the available evidence that may support or refute each of these claims in turn.

Hypothesis 1: Are *BRCA1* alterations less often germline lesions than *BRCA2* alterations? This does not seem to be the case. In the TRITON2 study,² there were equal proportions of germline alterations affecting the two genes (38% of *BRCA1* mutations [five of 13] and 38% of *BRCA2* mutations [39 of 102] were of germline origin). An equal frequency of germline mutations involving *BRCA1* and *BRCA2* in patients with mCRPC (about 50% for both genes) was also reported in another recent study.⁴ However, in the largest pan-cancer analysis of *BRCA1/2* alterations published to date (which included 7,185 prostate cancers) by Sokol et al,⁵ it was shown that germline mutations affected 35% of patients with *BRCA1*-altered mCRPC compared with 50% of patients with *BRCA2*-altered mCRPC. Thus, although it is possible that *BRCA2* alterations might be slightly enriched for germline mutations compared with *BRCA1* alterations, this difference is likely to be small at best.

Hypothesis 2: Are *BRCA1* alterations less often biallelic mutations than *BRCA2* alterations? Yes, this seems to be correct. In the TRITON2 trial, only 40% of *BRCA1* mutations (two of five) that were evaluable for zygosity status were biallelic alterations, whereas 85% of evaluable *BRCA2* mutations (34 of 40) were biallelic alterations.² Similarly, in another recent study,⁴ the proportion of patients with germline-altered mCRPC who had somatic biallelic mutations

(as evidenced by tumoral loss of heterozygosity [LOH]) was 50% in *BRCA1* carriers and 60% in *BRCA2* carriers. Finally, in the large pan-cancer *BRCA1/2* analysis by Sokol et al,⁵ biallelic inactivation occurred in only 50% of *BRCA1* mutations versus 90% of *BRCA2* mutations; biallelic alteration was more common in both cases with germline mutation origin. Therefore, biallelic mutations in prostate cancer seem to involve *BRCA2* more commonly than *BRCA1*.

Hypothesis 3: Do *BRCA1* mutations result in attenuated HRR deficiency compared with *BRCA2* mutations? This is not likely. Because the efficacy of PARP inhibitors relies on impaired HRR function to induce synthetic lethality,⁶ a functional assessment of HRR deficiency or proficiency could theoretically predict sensitivity to PARP inhibition. With respect to the *BRCA1/2* genes, however, there is no evidence of differential HRR dysfunction when comparing alterations in the two genes. In one study that computed homologous recombination deficiency scores,⁴ the authors showed that prostate cancers with biallelic *BRCA1* and *BRCA2* mutations had similar composite homologous recombination deficiency scores, and these scores were in fact slightly higher in *BRCA1*-altered prostate cancers. Similarly, in another study that examined genome-wide LOH (gLOH) scores as a surrogate for HRR function,⁵ biallelic *BRCA1* and *BRCA2* mutations were associated with high gLOH scores in 40% and 25% of prostate cancers, respectively; the proportion of the cancer genome under LOH (% gLOH) was slightly higher in prostate tumors with biallelic *BRCA1* versus *BRCA2* mutations (15% v 10%, respectively). In sum, this suggests that biallelic inactivation of *BRCA1* does indeed result in significant HRR deficiency and that perhaps we need better ways to define true *BRCA1* loss in prostate cancer. In other malignancies, for example, *BRCA1* methylation has been associated with PARP inhibitor sensitivity,⁷ whereas mutations in exon 11 of *BRCA1* may predict therapeutic resistance to PARP inhibition.⁸

Hypothesis 4: Do *BRCA1*-mutated cancers have more genomic co-alterations (eg, in *TP53* or *PTEN*) than *BRCA2*-mutated cancers? This seems to be the case, at least for mutations in *TP53*. It could also be hypothesized that *BRCA1/2*-altered prostate cancers with concurrent mutations in other genes associated with poor prognosis (eg, *TP53* or *PTEN*)^{9,10} might demonstrate attenuated sensitivity to PARP inhibitors, and we wondered whether such mutations might be distributed unequally in the two groups. In the TRITON2 study,² for example, it was observed that patients with *BRCA1* mutations had more frequent co-alterations in *TP53* (62%) and *PTEN* (69%) compared with those who had *BRCA2* mutations (*TP53* alterations in 42% and *PTEN* alterations in 29%, respectively). To determine whether these findings were real or spurious, we analyzed publicly available genomic data from the cBioPortal repository.¹¹ We discovered that deleterious *TP53* alterations were significantly more frequent in *BRCA1*-mutated versus *BRCA2*-mutated prostate cancers (39% [19 of 49] v

23% [76 of 336], respectively; $P = .02$), whereas the prevalence of deleterious *PTEN* alterations was similar (20% [10 of 49] v 18% [59 of 336], respectively; $P = .69$). Intriguingly, *TP53* (but not *PTEN*) co-alterations were also more common in *BRCA1*-altered versus *BRCA2*-altered breast cancer (66% [78 of 119] v 35% [57 of 165], respectively; $P < .01$) and bladder cancer (58% [14 of 24] v 34% [20 of 58]; $P = .05$), as well as colorectal (56% [19 of 34] v 36% [32 of 88]; $P = .06$), gastroesophageal (36% [29 of 81] v 26% [111 of 421]; $P = .10$), endometrial (55% [12 of 22] v 34% [24 of 71]; $P = .13$), and even cutaneous squamous cell carcinomas (42% [22 of 52] v 23% [78 of 338]; $P = .01$). In addition to *TP53* alterations broadly portending an overall worse prognosis, recent reports suggest that *TP53* mutations might be more permissive of the emergence of *BRCA1/2* reversion mutations (that restore the open reading frame) in *BRCA1/2*-altered cancers exposed to PARP inhibitor treatment.^{4,12} Such reversion mutations have been associated with secondary PARP inhibitor resistance in prostate and other cancers.

Ultimately, because of the relative rarity of both germline and somatic *BRCA1* mutations compared with *BRCA2* mutations in prostate cancer^{10,13} (unlike the situation in breast or ovarian cancers, where the prevalence of two genes is roughly equal), our conclusions related to PARP inhibitor sensitivity should be interpreted with caution. As presented in Table 1, the total number of patients with *BRCA1*-altered mCRPC included in the publicly available global literature is a mere 21 patients, which limits making robust conclusions. Additional studies and meta-analyses will be required to gain clearer insights on the potential differential efficacy of PARP inhibitors in prostate cancers with *BRCA1* versus *BRCA2* mutations and to understand the biologic mechanisms underpinning this phenomenon. At this time, both rucaparib and olaparib are indicated, and should be considered, for the treatment of mCRPC patients with either *BRCA1* or *BRCA2* mutations. Indeed, the availability of genomically selected therapies for our patients with *BRCA1/2*-altered advanced prostate cancer represents a welcome addition to our therapeutic armamentarium and is a giant step forward in the management of this disease.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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