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Differential Response to Olaparib Treatment Among Men with Metastatic Castration-resistant Prostate Cancer Harboring *BRCA1* or *BRCA2* Versus *ATM* Mutations

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Abstract

Background: Poly ADP-ribose polymerase (PARP) inhibitors, such as olaparib, are being explored as a treatment option for metastatic castration-resistant prostate cancer (mCRPC) in men harboring mutations in homologous recombination DNA-repair genes. Whether responses to PARP inhibitors differ according to the affected gene is currently unknown.
Objective: To determine whether responses to PARP inhibitors differ between men with *BRCA1/2* and those with *ATM* mutations.
Design, setting, and participants: This was a multicenter retrospective review of 23 consecutive men with mCRPC and pathogenic germline and/or somatic *BRCA1/2* or *ATM* mutations treated with olaparib at three academic sites in the USA.
Outcome measurements and statistical analysis: The proportion of patients achieving a $\geq$50% decline in prostate-specific antigen (PSA_{50} response) was compared using Fisher's exact test. Clinical and radiographic progression-free survival (PFS) and overall survival were estimated using Kaplan-Meier analyses and compared using the log-rank test.
Results and limitations: The study included two men with *BRCA1* mutations, 15 with *BRCA2* mutations, and six with *ATM* mutations. PSA_{50} responses to olaparib were achieved in 76% (13/17) of men with *BRCA1/2* versus 0% (0/6) of men with *ATM* mutations (Fisher's exact test; $p = 0.002$). Patients with *BRCA1/2* mutations had median PFS of 12.3 mo versus 2.4 mo for those with *ATM* mutations (hazard ratio 0.17, 95% confidence interval 0.05–0.57; $p = 0.004$). Limitations include the retrospective design and relatively small sample size.
Conclusions: Men with mCRPC harboring *ATM* mutations experienced inferior outcomes to PARP inhibitor therapy compared to those harboring *BRCA1/2* mutations. Alternative therapies should be explored for patients with *ATM* mutations.
Patient summary: Mutations in *BRCA1/2* and *ATM* genes are common in metastatic prostate cancer. In this study we compared outcomes for men with *BRCA1/2* mutations to those for men with *ATM* mutations being treated with olaparib. We found that men with *ATM* mutations do not respond as well as men with *BRCA1/2* mutations.

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1. Introduction

While there are currently seven therapies approved by the US Food and Drug Administration (FDA) for the treatment of metastatic castration-resistant prostate cancer (mCRPC), which is the lethal form of the disease, there are few genetic biomarkers to predict an individual's response to therapy. In ovarian and breast cancer, poly ADP-ribose polymerase (PARP) inhibitors are used for patients harboring germline mutations in *BRCA1* or *BRCA2*, supporting the concept of synthetic lethality [1]. Across all solid tumor types, the presence of mismatch repair (MMR) gene mutations predicts sensitivity to immune checkpoint blockade [2].

Although there are many molecular determinants of prostate cancer, few have given rise to genomically targeted therapies [3]. The FDA recently granted "breakthrough" designation status to the PARP inhibitor olaparib for treatment of mCRPC patients harboring germline and/or somatic mutations in the DNA-repair genes *BRCA1* and *BRCA2*, as well as *ATM* [4]. This decision was based on earlier trials suggesting that men with mCRPC harboring mutations in homologous recombination DNA-repair genes are more likely to respond to olaparib than men without such mutations [5,6]. More recently, FDA "breakthrough" status was also granted to another PARP inhibitor, rucaparib, for mCRPC patients with *BRCA1/2* mutations [7]. However, because *ATM* functions as a sensor of DNA damage rather than a mediator of DNA repair [8], we hypothesized that patients harboring *ATM* mutations might not show the same responses to PARP inhibitor therapy as those harboring *BRCA1/2* mutations (which are bona fide homologous recombination genes) [9]. Here we describe the differential response to treatment with the PARP inhibitor olaparib among men with *BRCA1/2* versus *ATM* mutations.

2. Patients and methods

This was a retrospective observational study of 46 consecutive patients with progressive mCRPC who were prescribed off-label single-agent olaparib at Johns Hopkins Hospital, University of Washington, and Mayo Clinic–Scottsdale from December 2014 (the date of olaparib FDA approval for ovarian cancer [10]) through October 2018. Patients who were deemed fit for therapy and were ineligible, declined, or did not have access to a clinical trial with PARP inhibitors were offered therapy. Those harboring pathogenic mutations (somatic or germline) in *BRCA1*, *BRCA2*, or *ATM* were included in this analysis. All centers participating in the study obtained local institutional review board approval before data abstraction.

Demographic, clinical, and genomic data were recorded and reported. Proportions were compared using a χ^2 or Fisher's exact test, while means were compared using a Kruskal-Wallis test.

The primary efficacy endpoint was the percentage of men achieving a $\geq$50% decline in prostate-specific antigen level from baseline (PSA_{50} response). Response rates were compared between men with *BRCA1/2* mutations and men with *ATM* mutations using Fisher's exact test. Radiographic or clinical progression-free survival (PFS) and overall survival (OS) were estimated using Kaplan-Meier analysis and comparisons between mutational groups were carried out using log-rank testing. Clinical or radiographic progression was defined as either radiologic progression or unequivocal clinical progression (or death), whichever occurred first. Radiographic progression was determined at the discretion of the local radiologists, broadly consistent with the Prostate Cancer clinical trials Working Group 3 (PCWG3) guidelines [11]. Clinical progression was defined as worsening bone pain, a need for additional systemic or radiation therapy, or bone complications including fracture or spinal cord compression. Patients were followed from the time of olaparib initiation until the time of last clinical or radiographic assessment for PFS and were censored at the time of last

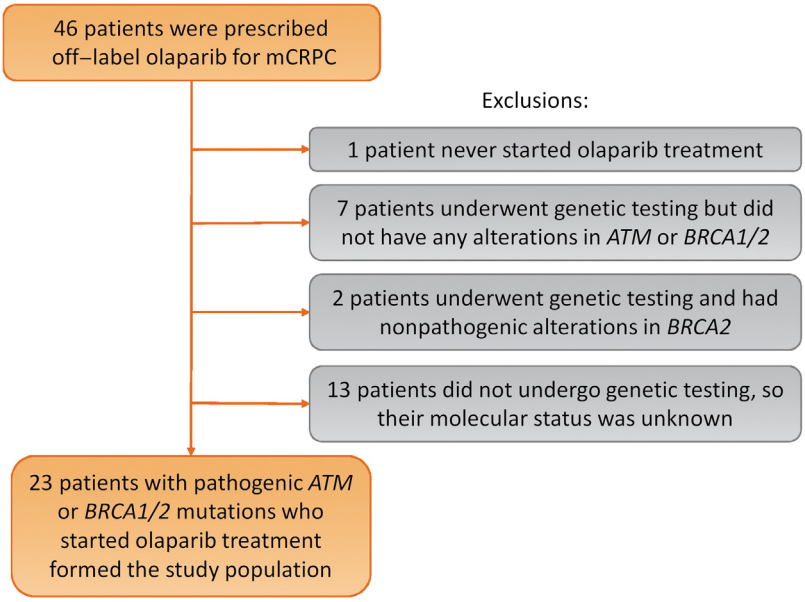

Fig. 1 – Consort diagram. mCRPC = metastatic castration-resistant prostate cancer.

Table 1 – List of pathogenic mutations in *BRCA1/2* or *ATM* observed in our cohort

ID	Gene	Mutation			Platform used for detection
		Origin	Name	Mechanism	
1	*BRCA2*	Somatic	p.N899I fs*5; p.K1691N fs*15	Frameshift deletions	PGDx-Cancer Select
2	*BRCA2*	Germline	p.Y2215S fs*13	Frameshift deletion	Color Genomics
3	*ATM*	Germline	p.S1905I fs*25	Frameshift insertion	Color Genomics
4	*BRCA2*	Germline	p.N319K fs*8	Frameshift insertion	Color Genomics
5	*BRCA2*	Germline	p.D3095E	Missense	Color Genomics
6	*ATM*	Somatic	p.Q284X*	Nonsense	PGDx-Plasma Select
7	*BRCA2*	Germline	p.D156X*	Nonsense	Color Genomics
8	*BRCA2*	Germline	p.W1692M fs*3	Frameshift insertion	Color Genomics
9	*BRCA2*	Somatic	p.S1982R fs*22	Frameshift deletion	Foundation One
10	*BRCA1*	Germline	p.Y1463X*	Nonsense	Color Genomics
11	*BRCA1*	Germline	c.4357+1G>A	Splicing	Color Genomics
12	*ATM*	Somatic	Loss of exons 30-34	Rearrangement	Foundation One
13	*BRCA2*	Germline	p.S3147C fs*2	Frameshift deletion	Myriad genetics
14	*BRCA2*	Germline	p.Q2858A fs*5	Frameshift insertion	Caris Genetics
15	*BRCA2*	Somatic	p.F1546L fs*22	Frameshift deletion	Foundation One
16	*ATM*	Somatic	p.M1V	Missense	Foundation One
17	*ATM*	Somatic	p.N405K fs*15	Frameshift deletion	Foundation One
18	*ATM*	Somatic	1.7 kbp deletion	Rearrangement	UW-Oncoplex
19	*BRCA2*	Germline	p.L1908R fs*2	Frameshift deletion	Myriad genetics
20	*BRCA2*	Germline	p.T2125P fs*12	Frameshift deletion	Color Genomics
21	*BRCA2*	Germline	Exon loss, with hemizygous deletion of somatic allele	Rearrangement	Stand Up 2 Cancer (MI-OncoSeq)
22	*BRCA2*	Somatic	Homozygous deletion	Rearrangement	Stand Up 2 Cancer (MI-OncoSeq)
23	*BRCA2*	Somatic	Homozygous deletion	Rearrangement	UW-Oncoplex

Table 2 – Baseline demographic and clinical data overall and by mutation type

	Overall	*ATM*	*BRCA1/2*	*p* value
Patients, *n* (%)	23	6 (26)	17 (74)	
Gleason sum at diagnosis, *n* (%)				0.8
7	9 (39)	2 (33)	7 (41)	
8	4 (17)	2 (33)	2 (12)	
9	9 (39)	2 (33)	7 (41)	
Unavailable	1 (4)	0 (0)	1 (6)	
Median age at start of therapy, yr (IQR)	66 (61–71)	71 (70–76)	65 (61–70)	0.07
Median baseline PSA, ng/ml (IQR)	37 (6.2–281)	278 (95.2–365)	22 (5.4–53.9)	0.06
Prior chemotherapy, *n* (%)				1
Yes	15 (65)	4 (67)	11 (65)	
No	8 (35)	2 (33)	6 (35)	
Prior enzalutamide/abiraterone, *n* (%)				0.5
Yes	21 (91)	5 (83)	16 (94)	
No	2 (9)	1 (17)	1 (6)	
Type of mutation, *n* (%)				0.052
Germline	13 (57)	1 (17)	12 (71)	
Somatic	10 (43)	5 (83)	5 (29)	
Presence of bone metastases, *n* (%)				0.5
Yes	20 (87)	6 (100)	14 (82)	
No	3 (13)	0 (0)	3 (18)	
Presence of visceral metastases, *n* (%)				0.1
Yes	6 (26)	0 (0)	6 (35)	
No	17 (74)	6 (100)	11 (65)	
Presence of nodal metastases, *n* (%)				1
Yes	13 (52)	3 (50)	10 (59)	
No	10 (48)	3 (50)	7 (41)	
Mean prior TLs for mCRPC, *n* (range)	2.9 (0–5)	2.8 (0–4)	2.9 (1–5)	0.7
Mean TLs after olaparib, *n* (range)	0.70 (0–4)	0.83 (0–2)	0.65 (0–4)	0.4

IQR = interquartile range; mCRPC = metastatic castration-resistant prostate cancer; PSA = prostate-specific antigen; TL = treatment line.

contact with the health system for OS. Stata version 15 (StataCorp, College Station, TX, USA) was used for statistical analyses.

3. Results

3.1. Cohort characteristics

Forty-six men received off-label olaparib treatment (300 mg orally twice daily) for mCRPC during the study period and were included in this study (Fig. 1). Thirteen patients did not undergo any genetic testing, seven patients underwent genetic testing that revealed no known *ATM*, *BRCA1*, or *BRCA2* gene mutations, two patients had nonpathogenic mutations (silent variants) in *BRCA2*, and one patient was prescribed but did not start olaparib. These patients were not included in this analysis, as those without pathogenic DNA repair gene mutations would not be expected to benefit from PARP inhibitor treatment given current knowledge. Twenty-three patients had pathogenic mutations in *BRCA1/2* (n = 17) or *ATM* (n = 6) and were included in this analysis (Table 1). Thirteen (57%) of these mutations were of germline and ten (43%) were of somatic origin. Table 2 displays the baseline clinical and demographic characteristics of the 23 patients. Patients with an *ATM* mutation did not significantly differ from those with a *BRCA1/2* mutation other than a trend towards more germline mutations in the *BRCA1/2* cohort and more bone-only disease in the *ATM* cohort. At diagnosis, nine (39%), four (17%), and nine (39%) patients had Gleason sum 7, 8, and 9, respectively. The median age at time of olaparib initiation was 66 yr (interquartile range [IQR] 61–71). The median baseline PSA level was 37 ng/ml (IQR 6–281). The median time on olaparib treatment was 5.4 months (mo) (IQR 2.6–11.2), with six *BRCA2*-positive patients continuing on therapy at the time of database lock. The median time on therapy for patients with *ATM* mutations

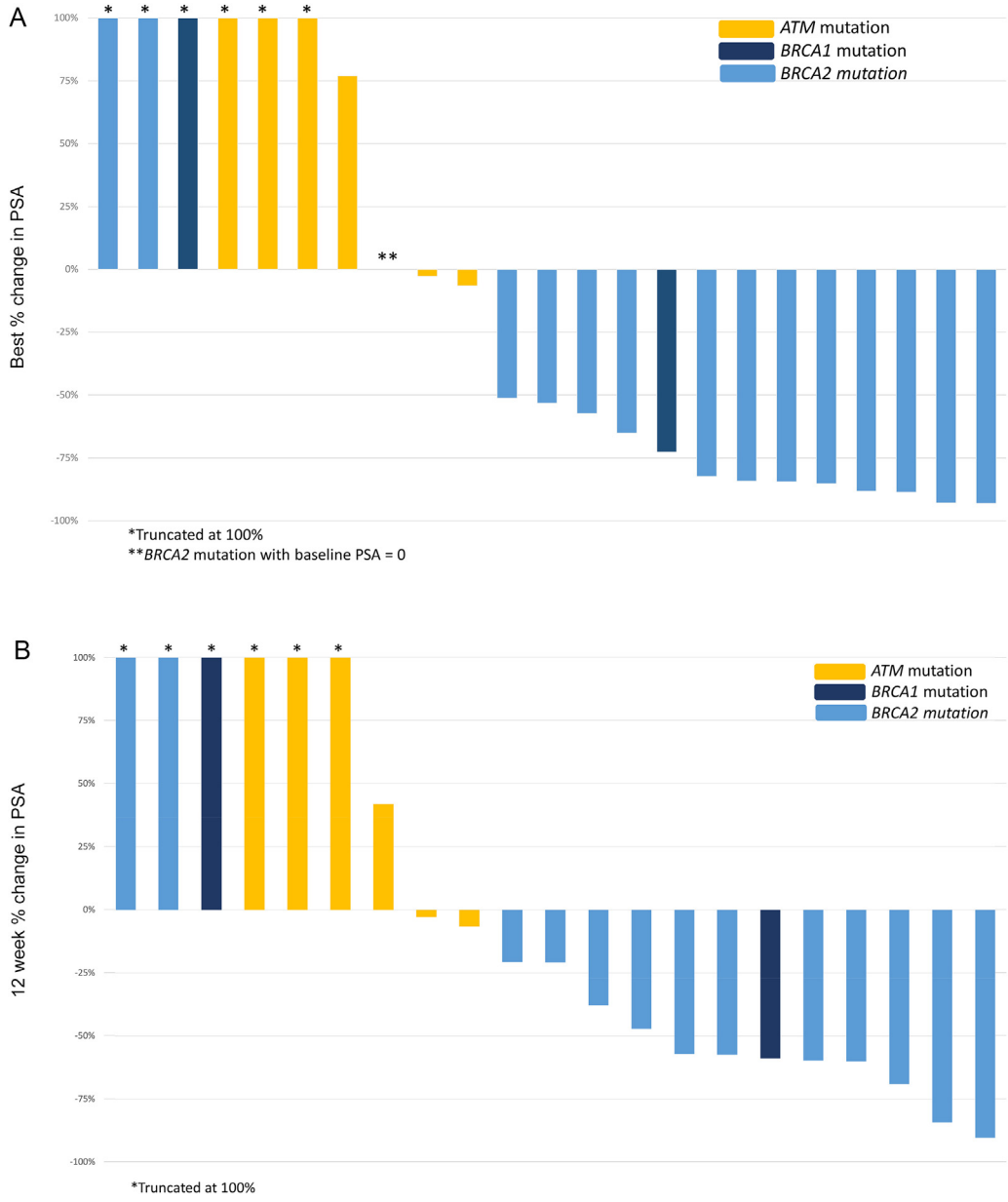

Fig. 2 – Best prostate-specific antigen (PSA) response by mutation status (A) at any time and (B) at 12 wk.

was 2.6 mo (IQR 2.4–4.7) versus 8.4 mo (IQR 4.2–11.9) for those with *BRCA1/2* mutations.

3.2. PSA response rates

Fig. 2A shows the best PSA response for each patient at any time point. Overall, 13/23 patients (57%) achieved a PSA_{50} response. No PSA responses (0/6) were observed among patients harboring *ATM* mutations, while 76% (13/17) of those with *BRCA1/2* mutations achieved a PSA_{50} response (-$p = 0.002$). The median time to best PSA response was 20 weeks (wk) (IQR 7–35). The 12-wk PSA response is reported in Fig. 2B; two patients could not be evaluated as they did not have PSA measured at the 12-wk time point (±4 wk). At 12 wk, 53% of the *BRCA1/2* cohort (8/15) achieved a PSA_{50} response versus 0% of ATM cohort (zero/six; $p = 0.046$).

3.3. PFS and OS

Overall, 17/23 patients had clinical or radiographic progression, all six of those with *ATM* mutations and 11/17 patients with *BRCA1/2* mutations. Clinical or radiographic PFS with olaparib was significantly longer among patients with *BRCA1/2* mutations than among those with *ATM* mutations (Fig. 3A). Men with *BRCA1/2* mutations had a median PFS of 12.3 mo, compared to 2.4 mo in the *ATM* group (hazard ratio [HR] 0.17, 95% confidence interval [CI] 0.05–0.57; $p = 0.004$). The median time to last assessment of progression for those who did not experience progression was 8 mo.

Nine patients (three with *ATM* and six with *BRCA1/2* mutations) died during follow-up. OS was longer in the *BRCA1/2* cohort than in the *ATM* cohort (29.8 vs 4.1 mo; HR 0.14, 95% CI 0.02–0.88; $p = 0.04$; Fig. 3B). The median time to last assessment among those still living was 9.4 mo.

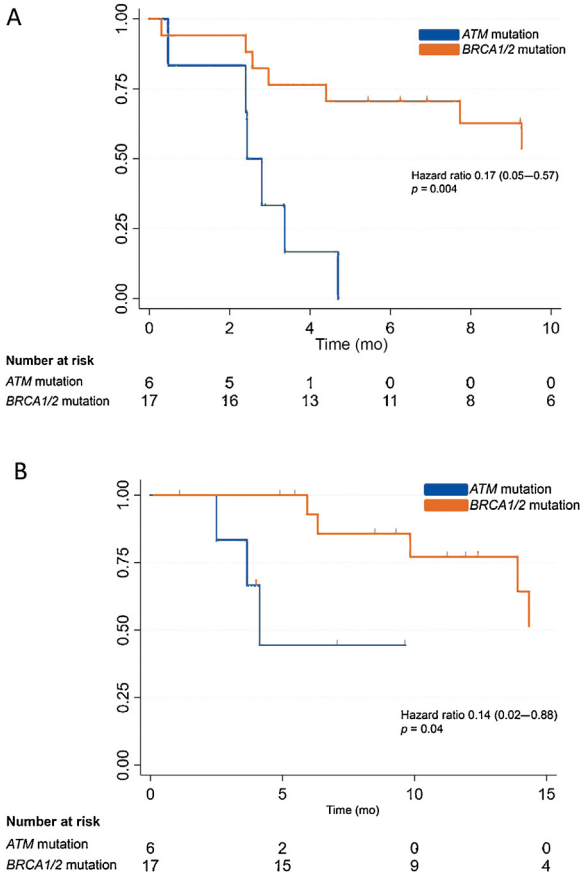

Fig. 3 – Kaplan-Meier curve for (A) progression-free survival (the *x*-axis is truncated at 10 mo) and (B) overall survival (the *x*-axis is truncated at 15 mo) by mutation status.

4. Discussion

Our results suggest that men with mCRPC harboring *ATM* mutations may not respond to PARP inhibitors as well as those with *BRCA1/2* mutations. A similar pattern was recently observed in the preliminary results of the TRITON2 study (Trial of Rucaparib in Prostate Indications 2) investigating rucaparib, in which none of the 18 patients with *ATM* mutations demonstrated a PSA_{50} response, compared to 51% (23/45) of those with *BRCA1/2* mutations [12]. This is seemingly in contrast to the TOPARP-A study (Phase II Trial of Olaparib in Patients with Advanced Castration Resistant Prostate Cancer - Part A), in which four of six patients (67%) with *ATM* mutations responded to olaparib, although only two of the six patients achieved a PSA_{50} response at 12 wk, with the other two only achieving a decrease in circulating tumor cells [5]. It is also important to note that the time to best PSA response may be delayed (median of 20 wk in our study) and that five patients only achieved a PSA_{50} response after 12 wk. This should be taken into consideration when interpreting future studies, and suggests that early PSA responses may not be the optimal measure of clinical benefit for PARP inhibitor therapy in prostate cancer.

One plausible biological mechanism explaining why men harboring *BRCA1/2* mutations may respond differently to PARP inhibitors compared to those with *ATM* mutations is that the ATM protein functions primarily as a sensor of DNA damage rather than an effector of DNA repair like *BRCA1* and *BRCA2* [13]. Studies in breast cancer patients harboring germline *ATM* mutations have shown that *ATM*-mutant cancers are molecularly distinct from *BRCA1/2*-mutant cancers, lack characteristic genomic features reflective of homologous recombination deficiency, and exhibit significantly different immune infiltrates compared to *BRCA1/2*-mutant cancers [8]. Similar findings have been observed in prostate cancer: *ATM*-mutant tumors showed a distinct transcriptional phenotype compared to tumors with mutations in true homologous repair genes [14]. A second potential explanation is that optimal response to PARP inhibitors probably requires biallelic gene inactivation for induction of synthetic lethality. In this context, *BRCA1/2* mutation carriers may have a higher degree of biallelic loss than those with *ATM* mutations [15,16]. Furthermore, germline mutation carrier status, which was more prevalent in the *BRCA1/2* group, may be relevant because every cancer cell will have at least monoallelic inactivation, whereas in patients with only somatic mutations, there may be only a tumor subclone that carries the mutation.

Taken together, our data suggest that alternative treatment strategies are needed for mCRPC patients harboring *ATM* mutations, as these men exhibit unfavorable responses to PARP inhibitors, progress relatively quickly, and are therefore not deriving significant benefit from therapy in comparison to those with *BRCA1/2* mutations. Differing response rates to abiraterone and enzalutamide in *ATM*- and *BRCA*-deficient patients have also been observed in some studies [17,18]. Additional treatments such as ATR inhibitors have emerged as potential therapeutic approaches specifically for *ATM*-mutant cancers, including prostate cancers [19,20].

The limitations of this study include its retrospective nature with overall small sample size determined post hoc. In addition, this is a real-world experience with PARP inhibitors and does not control for many of the known and unknown baseline factors that may differ between the groups. Finally, we were not able to reliably assess biallelic mutations in most patients given the clinical-grade genomic assays used and were not able to perform immunohistochemical staining for BRCA1/2 or ATM protein loss.

5. Conclusions

Larger prospective studies are needed to confirm these preliminary findings. In addition, as these mechanisms are not unique to prostate cancer, similar findings should be explored in other cancer types for which PARP inhibitors are being used.

Author contributions: Emmanuel S. Antonarakis had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Antonarakis, Marshall, Bryce.
Acquisition of data: Marshall, Sokolova, McNatty, Bryce, Antonarakis, Cheng, Eisenberger, Schweizer.
Analysis and interpretation of data: Marshall, Sokolova, McNatty, Bryce, Antonarakis, Cheng, Eisenberger, Schweizer.
Drafting of the manuscript: Marshall, Antonarakis.
Critical revision of the manuscript for important intellectual content: Marshall, Sokolova, McNatty, Bryce, Antonarakis, Cheng, Eisenberger, Schweizer.
Statistical analysis: Marshall, Antonarakis.
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