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Platinum Opinion

Untangling the PROfound Trial for Advanced Prostate Cancer: Is There Really a Role for Olaparib?

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Multiple therapies are used in standard-of-care treatment for patients with metastatic castration-resistant prostate cancer (mCRPC), including the androgen signaling inhibitors (ASIs) abiraterone and enzalutamide, and the taxanes docetaxel and cabazitaxel. Despite these advances, mCRPC remains an incurable disease with median survival of 2 yr in routine practice [1]. On May 19, 2020, the US Food and Drug Administration (FDA) approved the PARP inhibitor olaparib for patients with mCRPC and mutations in homologous recombination repair (HRR) genes after progression on abiraterone or enzalutamide. This decision was based on interim analyses of the phase 3 PROfound trial [2]. In this commentary, we review methodological concerns with this trial and discuss whether olaparib should be a standard-of-care treatment in this population.

The PROfound trial evaluated the efficacy of olaparib for mCRPC with an alteration in prespecified HRR genes. Patients who progressed on abiraterone or enzalutamide were randomized to olaparib or physician's choice of abiraterone or enzalutamide. PROfound met its primary endpoint of radiographic progression-free survival (rPFS) in two populations: cohort A, consisting of patients with *BRCA1*, *BRCA2*, or *ATM* mutations (median 7.4 mo vs 3.6 mo; hazard ratio [HR] for progression or death 0.34, 95% confidence interval [CI] 0.25–0.47); and cohorts A + B, which included patients with other HRR mutations (5.8 mo vs 3.5 mo; HR for progression or death 0.49, 95% CI 0.38–0.63). Overall survival (OS), a secondary endpoint, was numerically longer in the olaparib arm than in the control group in cohort A (18.5 mo vs 15.1 mo; HR for death 0.64, 95% CI 0.43–0.97) and cohorts A + B (17.5 mo vs 14.3 mo; HR for death 0.67, 95% CI 0.49–0.93); however, these differences did not meet protocol-specified statistical significance. The objective response rate (ORR) and prostate-specific antigen (PSA) response rate were higher in the olaparib arm compared to investigator's choice. While these results appear promising, we have four fundamental concerns with PROfound: (1) a suboptimal control arm; (2) use of crossover; (3) use of rPFS as the primary endpoint; and (4) merging of cohorts A + B for analyses.

1. Is the control arm appropriate?

The control arm of abiraterone or enzalutamide (presumably whichever had not been used earlier—and, of concern, 18% of participants had received both) is suboptimal since there is substantial cross-resistance between these agents, leading to poor response rates and short PFS [3–5]. The PSA response rate in the control arm was predictably low (10%). One-third of participants did not have prior docetaxel and ~80% had not received cabazitaxel, both of which offer OS and quality-of-life benefits [6,7]. A true "physician's choice" control arm would have included (and recommended) these agents, perhaps with the option of platinum given its activity in small trials for mCRPC and general activity against cancers with DNA repair deficiency [8].

The control arm in PROfound is not consistent with the TOPARP-A phase 2 trial that preceded phase 3 testing of olaparib in this setting, in which all participants had prior taxane therapy [9]. For PROfound, the authors attempt to justify the control arm by citing low response rates to taxane therapy after ASI and the fact that almost half of patients in "routine practice" do not receive a taxane, according to a single-institution series of 119 patients [10]. However, the participants in PROfound are probably very different from those reported in a small single-center case series: if they were fit enough to receive olaparib,

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almost all would have been fit enough to receive a taxane. Most men in the control arm of PROfound received substandard therapy.

2. When is the use of crossover appropriate?

In PROfound, men in the control arm were permitted to cross over to olaparib treatment on progression, and 82% of them did so. As a general rule, crossover is desirable in trials that seek to move an established drug to earlier lines of therapy (ie, comparing routine upfront use to salvage use). Crossover is undesirable in trials seeking to establish the fundamental efficacy of novel therapies [11].

As a result of crossover in PROfound, many men in the control arm waited twice for taxane therapy (first while receiving an ASI, and then while on olaparib). Crossover results in ambiguity as to whether the OS difference is attributable to effective treatment or to a delay in other effective therapies occurring disproportionately among patients in the control arm. Because subsequent lines of therapy are not described in the publication, it is not feasible to identify whether men received appropriate postprotocol therapy.

3. Is rPFS an appropriate primary endpoint?

The essential outcome measures showing benefit in a phase 3 trial are OS and its quality, and it is laudable that most previous trials for men with mCRPC have defined OS as the primary endpoint [7,12–16]. Although some studies have examined the correlation between rPFS and OS, there is no robust (trial-level) analysis showing that rPFS is a valid surrogate endpoint for OS or quality of life in the setting of mCRPC [17]. Although numerical OS differences were observed between the experimental and control arms for cohort A and cohorts A + B of PROfound, these differences did not meet the prespecified interim analysis α level of 0.01. The OS results, albeit with immature data, should be interpreted with caution, especially since postprotocol therapies were not described and are probably imbalanced.

4. What are the outcomes for cohort B?

Analysis for cohort B, a genetically heterogeneous group of men whose tumors had mutations in 12 prespecified genes, was only reported in the Supplementary material for PROfound, without statistical analysis. Crossing rPFS curves with a small rPFS benefit in cohort B suggest that cohort A drove the rPFS improvement demonstrated for cohorts A + B. The use of olaparib in patients with mCRPC and HRR mutations other than *BRCA1*, *BRCA2*, and *ATM* is therefore unsubstantiated, and it is concerning that FDA approval was granted for cohorts A + B.

5. Where do we go from here?

Olaparib is a very expensive treatment that is priced at more than $12 000 per month [18]. Somatic sequencing and/or germline testing are required to detect HRR mutations, which are present in only 22% of patients with mCRPC [19]. It is difficult to justify these costs when considering the design flaws of the PROfound trial. Docetaxel, by contrast, is approximately one-third of the price of this agent [18].

Instead of PROfound, a trial is needed to compare olaparib with a true investigator's choice. This would include taxanes (for those who had not received them) and platinum, which has a promising PSA response rate of >50% in HRR-mutated mCRPC [19]. The central question is whether having olaparib in the clinical "toolbox" can improve quantity or quality of life for this population. Unfortunately, the limitations of PROfound prevent us from knowing the answer.

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References

[1] George DJ, Sartor O, Miller K, et al. Treatment patterns and outcomes in patients with metastatic castration-resistant prostate cancer in a real-world clinical practice setting in the United States. Clin Genitourin Cancer 2020;18:284–94. http://dx.doi.org/10.1016/j.clgc.2019.12.019.

[2] de Bono J, Mateo J, Fizazi K, et al. Olaparib for metastatic castration-resistant prostate cancer. N Engl J Med 2020;382:2091–102. http://dx.doi.org/10.1056/NEJMoa1911440.

[3] Noonan KL, North S, Bitting RL, Armstrong AJ, Ellard SL, Chi KN. Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. Ann Oncol 2013;24:1802–7.

[4] Smith MR, Saad F, Rathkopf DE, et al. Clinical outcomes from androgen signaling-directed therapy after treatment with abiraterone acetate and prednisone in patients with metastatic castration-resistant prostate cancer: post hoc analysis of COU-AA-302. Eur Urol 2017;72:10–3.

[5] Khalaf DJ, Annala M, Taavitsainen S, et al. Optimal sequencing of enzalutamide and abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer: a multicentre, randomised, open-label, phase 2, crossover trial. Lancet Oncol 2019;20:1730–9.

[6] Mottet N, Cornford P, van den Bergh RCN, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part 6.5.2: management of mCRPC – general aspects. European Association of UrologyArnhem, The Netherlands https://uroweb.org/guideline/prostate-cancer/#62020

[7] Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351:1502–12.

[8] Mota JM, Barnett E, Nauseef JT, et al. Platinum-based chemotherapy in metastatic prostate cancer with DNA repair gene alterations. JCO Precis Oncol 2020;4:355–66.

[9] Mateo J, Carreira S, Sandhu S, et al. DNA-repair defects and olaparib in metastatic prostate cancer. N Engl J Med 2015;373:1697–708.
[10] Steinberger AE, Ledet EM, Luk E, et al. Characterizations of clinical and therapeutic histories for men with prostate cancer-specific mortality. Clin Genitourin Cancer 2016;14:139–48.
[11] Haslam A, Prasad V. When is crossover desirable in cancer drug trials and when is it problematic? Ann Oncol 2018;29:1079–81.
[12] de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010;376:1147–54.
[13] Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411–22.
[14] Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med 2013;369:213–23.
[15] de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011;364:1995–2005.
[16] Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012;367:1187–97.
[17] Prasad V, Kim C, Burotto M, Vandross A. The strength of association between surrogate end points and survival in oncology: a systematic review of trial-level meta-analyses. JAMA Intern Med 2015;175:1389–98.
[18] Memorial Sloan Kettering Cancer Center. Cancer drug costs for a month of treatment at initial Food and Drug Administration approval. www.mskcc.org/sites/default/files/node/25097/documents/111516-drug-costs-table.pdf.
[19] Robinson D, Van Allen EM, Wu YM, et al. Integrative clinical genomics of advanced prostate cancer. Cell 2015;161:1215–28.