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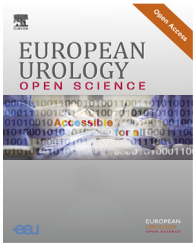

Brief Correspondence

Contextualizing Olaparib and Abiraterone in the Current Treatment Landscape for Metastatic Castration-resistant Prostate Cancer

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Abstract

The PROpel trial assessed the combination of olaparib + abiraterone acetate (AA) plus prednisone and androgen deprivation therapy (ADT) versus AA plus prednisone and ADT alone as first-line treatment for metastatic castration-resistant prostate cancer (mCPRP). To contextualize the progression free survival (PFS) benefit in PROpel, we performed a systematic review and quasi-individual patient data network meta-analysis on randomized controlled trials of first-line hormonal treatments for mCPRC. Meta-analysis was performed for the PROpel control arm and PREVAIL (enzalutamide) and COU-AA-302 (AA) treatment arms. Kaplan-Meier PFS curves were digitally reconstructed and differences in restricted mean survival time (ΔRMST) were computed. Combination therapy yielded longer PFS (24-mo ΔRMST 1.5 mo, 95% confidence interval 0.6–2.4) in comparison to novel hormonal treatments alone. However, the lack of mature overall survival data, higher complication rates, and higher health care costs are limitations of combination therapy. Ultimately, combining treatments, rather than molecularly targeted sequencing in cases of failure, might not be justified in unselected patients with mCRPC.

Patient summary: A recent trial showed that for metastatic prostate cancer that does not respond to hormone treatment, combined therapy with two drugs (olaparib and abiraterone) may prolong survival free from cancer progression. We included these data in an analysis of three trials that confirmed a small benefit. This combination approach has higher complication rates and is more expensive, and longer-term results for overall survival are needed.

The recently published PROpel trial assessed the role of olaparib + abiraterone acetate (abiraterone) plus prednisone in addition to androgen deprivation therapy (ADT) for patients with metastatic castration-resistant prostate cancer (mCRPC) who had not received any first-line treatment [1]. Patients were randomly assigned to receive either olaparib + abiraterone or abiraterone alone, irrespective of homologous recombination repair gene mutation (HRRm) status. The study showed longer progression-free survival (PFS) for patients receiving combination therapy in the form of olaparib and abiraterone in comparison to abiraterone alone [1]. Overall survival (OS) did not reach the prespecified threshold for significance but only 28.6% of the data were mature [1]. These

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encouraging results need to be evaluated in the current mCRPC treatment landscape.

Among the novel hormonal treatments for advanced prostate cancer, abiraterone and enzalutamide are approved as first-line options for mCRPC in light of practice-changing phase 3 studies [2,3]. In an effort to contextualize the PFS benefit observed in PROpel [1], we performed a systematic review and network meta-analysis (NMA) of randomized controlled trials on first-line treatments for mCPRC comparing novel hormonal treatment (abiraterone and enzalutamide) with PARP inhibitors according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses NMA guidelines [4].

Three randomized control trials were selected: PROpel [1], PREVAIL [2], and COU-AA-302 [3]. We digitalized the Kaplan-Meier curves for radiologic PFS from the three studies and reconstructed the survival data as previously described [5,6]. The control arms of PREVAIL and COU-AA-302 were not considered for the analyses as they consisted of ADT alone, which does not represent the standard of care for first-line treatment of mCRPC. In PROpel [1], patients assigned to the control arm received abiraterone in addition to ADT. For this reason, the meta-analysis was conducted for the control arm of PROpel [1] together with the treatment arms of PREVAIL [2], and COU-AA-302 [3], which consisted of enzalutamide and abiraterone, respectively, in addition to ADT.

Finally, we compared combination therapy to abiraterone or enzalutamide alone by evaluating differences in restricted mean survival time (ΔRMST) [5,6]. This represents the difference between the two integrals of the survivor functions up to a certain time point.

Descriptive characteristics of the studies are presented in Table 1. Not surprisingly, administration of combination therapy drove longer PFS (24-mo ΔRMST: 1.5 mo, 95% confidence interval 0.6–2.4) in comparison to novel hormonal treatments alone (Fig. 1). In the PROpel trial, there was no significant difference in OS and mature data are needed to conclude on whether a new treatment standard should be set. Therefore, OS data were not analyzed in the current study.

Although combination therapy demonstrated a PFS benefit, these results do have some limitations. First, while PREVAIL [2] and COU-AA-302 [3] were powered for both PFS and OS, PROpel [1] was powered only for PFS. Thus, a signal in terms of better OS in favor of combination therapy cannot be assumed. In this context, PFS has not been established as a reliable surrogate endpoint for OS in mCPRC. In fact, surrogacy according to the Prentice criterion has not yet been demonstrated, and thus the clinical significance of PFS in this setting has to be further investigated [7]. That being said, PFS is considered an important clinical parameter by the US Food and Drug Administration for medication approval, and correlation between PFS and OS in mCRPC

Table 1 – Study characteristics

	PROpel		COU-AA-302		PREVAIL	
	Ola + Abi	Abi + PB	Control	Abi	Enza	Control
Patients (*n*)	399	397	542	546	872	845
Age group, *n* (%)						
<65 yr	130 (33)[a]	97 (25)[a]	155 (29)	135 (25)	179 (21)	179 (21)
≥65 yr	269 (67)	300 (75)	387 (71)	411 (75)	693 (79)	666(79)
Race, *n* (%)						
White	282 (71)	275 (69)			669 (76.7)	655 (77.5)
Asian	66 (17)	72 (18)			85 (9.7)	82 (9.7)
Other					95 (10.9)	94 (11.1)
Black or African American	14 (4)	11 (3)			21 (2.4)	13 (1.5)
Native American or Alaska Native						
Not reported or unknown	37 (9)	39 (10)				
Gleason score, *n* (%)						
≤7			254 (50)	225 (46)	414 (49)	385 (48)
≥8	265 (66)	258 (65)	254 (50)	263 (54)	424 (51)	423 (52)
Data missing	13 (3)	5 (1)				
ECOG PS, *n* (%)						
0	286 (72)	272 (65)	414 (76)	416 (76)	584 (67)	585 (69)
1	112 (28)	124 (31)	128 (24)	130 (24)	288 (33)	260 (31)
Site of disease at baseline, *n* (%)						
Bone	349 (88)	339 (85)			741 (85.0)	690 (81.7)
Bone only			267 (49)	274 (51)	348 (39.9)	335 (39.6)
Lymph node	133 (33)	119 (30.0)	271 (50)	267 (49)	437 (50.1)	434 (51.4)
Soft tissue					517 (59.2)	504 (59.6)
Visceral[b]					98 (11.2)	106 (12.5)
Lung	40 (10)	42 (10)			64 (7.3)	75 (8.9)
Liver	15 (4)	18 (5)			40 (4.6)	34 (4.0)
Bone lesions at baseline, *n* (%)						
≤10 lesions					587 (67.2)	573 (67.8)
>10 lesions			253 (47)	264 (49)	285 (32.8)	172 (33.2)
Median PSA (ng/ml)	17.9	16.8	37.7	42.0	54.1	44.2

PSA = prostate-specific antigen; ECOG PS = Eastern Cooperative Oncology Group performance status; Ola = olaparib; Abi = abiraterone; Enza = enzalutamide; PB = placebo.

[a] Obtained as a difference from the originally reported data to the whole population.

[b] Liver or lung metastasis, only, as reported in the Prevail trial.

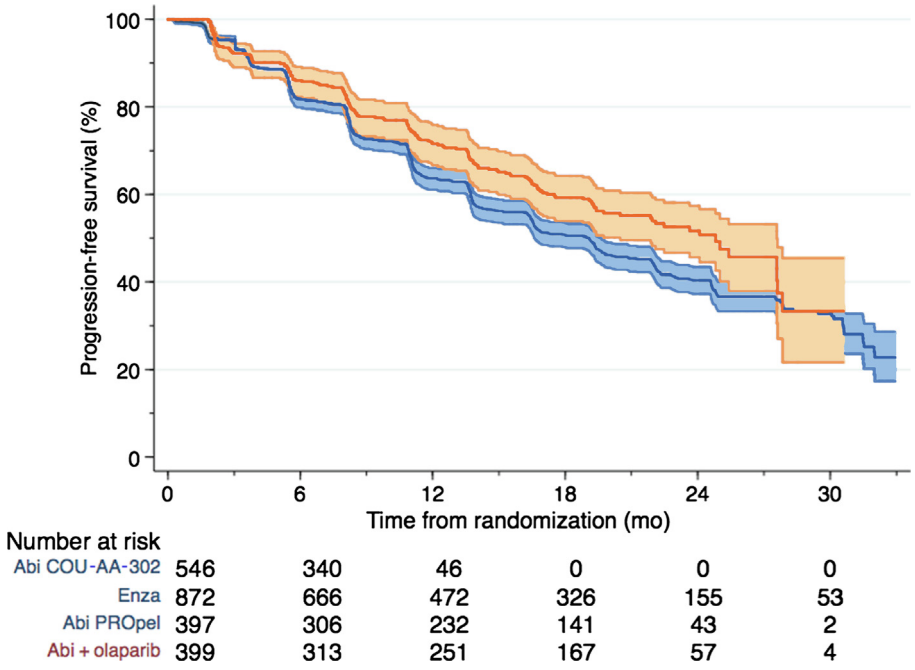

Fig. 1 – Progression-free survival from randomization to combination therapy (abiraterone [Abi] + olaparib) in comparison to hormonal therapies currently approved for metastatic castration-resistant prostate cancer (abiraterone [Abi] or enzalutamide [Enza] alone). Survival data were reconstructed from the PROpel, PREVAIL, and COU-AA-302 trials. The numbers at risk mirror one of the original studies, demonstrating precise reconstruction and allowing meaningful comparison.

might be inferred from previous studies [2,3,8]. Moreover, the clinical benefit in terms of months of PFS "gained" seems limited. On RMST analysis, we estimated a mean PFS gain of only 1.5 mo in favor of combination therapy versus abiraterone or enzalutamide alone, which is at the expense of higher toxicity, particularly anemia and pulmonary embolism, and health care costs.

Preliminary results from the MAGNITUDE trial were presented at the 2022 American Society of Clinical Oncology 2022 Genitourinary Symposium. The study had a similar design to PROpel [1] and the aim was to assess the role of niraparib + abiraterone acetate in men with mCRPC with or without HRRm [9]. Patients were randomly assigned to receive either niraparib + abiraterone or abiraterone alone. OS data are again immature in this trial; a PFS benefit emerged for the combination arm in a subgroup analysis for patients with alterations in HRR-associated genes, but not for unselected individuals. In PROpel, all subgroup analyses for the HRRm and non-HRRm groups showed a benefit with the abiraterone + olaparib combination versus abiraterone + placebo [1]. In addition, results from the TALAPRO-2 trial were recently released by Pfizer [10]. The study aim was to demonstrate an improvement in radiographic PFS for talazoparib + enzalutamide versus enzalutamide + placebo for men with mCRPC with or without HRRm. According to the press release, a PFS benefit and a trend towards better OS have been demonstrated. Comparison of individual patient data on completion of both trials is warranted to assess whether a patient subgroup might eventually benefit from combination therapy. Data from the CASPAR trial will also add much to the current literature.

Third, despite similarities in baseline patient characteristics (Table 1), there are some differences in the inclusion criteria: in PROpel, prior docetaxel use was permitted, during neoadjuvant/adjuvant treatment for localized prostate cancer and for metastatic hormone-sensitive prostate cancer. These differences hindered a fair comparison between the trials, but we still believe that NMA is the most meaningful way to compare trials in the same therapeutic setting, such as first-line treatment for mCRPC in this case.

In light of these data, combining treatments, rather than molecularly targeted sequencing at the time of failure, might not be justified in unselected patients with mCRPC. However, the benefit for selected cases such as individuals with HRRm or a high metastatic burden should be further evaluated in focused clinical studies. Mature OS data are needed before any definitive conclusion can be drawn regarding the potential role of combined olaparib + abirater one as first-line treatment for mCRPC.

Author contributions: Alberto Martini 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: Fallara, Martini, Robesti.
Acquisition of data: Fallara, Martini.
Analysis and interpretation of data: Fallara, Martini, Robesti.
Drafting of the manuscript: Fallara, Martini, Robesti.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Fallara, Martini.
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