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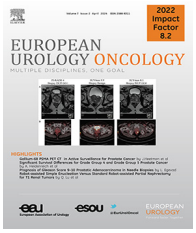

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Brief Correspondence

Olaparib plus Abiraterone for Metastatic Castration-resistant Prostate Cancer: Pharmacokinetics Data from the PROpel Trial

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Abstract

PROpel (NCT03732820) was a positive phase 3 trial that demonstrated a clinically significant improvement in radiographic progression-free survival with olaparib plus abiraterone versus placebo plus abiraterone in first-line metastatic castration-resistant prostate cancer. For a subset of PROpel patients, steady-state concentrations of olaparib, abiraterone, and Δ^4-abiraterone were measured in blood samples collected before and at several time points after dose administration. The pharmacokinetics (PK) for each drug and metabolite were evaluated to determine whether any clinically relevant drug-drug interactions between olaparib and abiraterone occurred. The results demonstrate that steady-state PK parameters for olaparib and abiraterone in PROpel were comparable with those in monotherapy trials. Abiraterone steady-state exposures were similar between treatment arms. Δ^4-Abiraterone had slightly lower steady-state exposures when abiraterone was administered in combination with olaparib. These results are consistent with a previous phase 2 study, supporting the conclusion that no clinically relevant PK-based drug-drug interactions occurred when olaparib and abiraterone were given in combination at their full monotherapy doses.

Patient summary: When drugs are administered in combination, a key consideration is whether there are any interactions between the drugs that may affect their activity. We analyzed blood concentrations of olaparib and abiraterone in a subset of patients with prostate cancer from the PROpel trial to determine if there were interactions between

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these two drugs. We found that there was no significant effect on the profile of either drug when they were given together at the same doses used when each drug is given individually.

PROpel, a global, randomized, double-blind, phase 3 trial (NCT03732820), met its primary endpoint, demonstrating a statistically significant improvement in radiographic progression-free survival (rPFS) in biomarker-unselected patients with first-line metastatic castration-resistant prostate cancer (mCRPC) treated with olaparib plus abiraterone versus placebo plus abiraterone. Median rPFS was 24.8 months (mo) versus 16.6 mo with placebo (hazard ratio 0.66, 95% confidence interval 0.54–0.81; $p < 0.001$) [1].

Olaparib and abiraterone are metabolized by CYP3A4/5, a cytochrome P450 enzyme responsible for metabolizing ~50% of marketed drugs. As olaparib is considered a weak CYP3A inhibitor and there is potential for abiraterone to inhibit CYP3A substrates [2,3], it is necessary to understand whether administration of these drugs in combination elicits any clinically relevant drug-drug interactions. While Δ^4-abiraterone is generally considered an important abiraterone metabolite, because of greater antitumor activity via inhibition of androgen receptor signaling [4], research has suggested that Δ^4-abiraterone might not make a meaningful contribution to the pharmacodynamic activity of abiraterone, and a high Δ^4-abiraterone/abiraterone metabolic ratio may in fact be associated with poorer clinical outcomes [5]. Monitoring of Δ^4-abiraterone pharmacokinetics (PK) was therefore necessary to understand this relationship.

A previous phase 2 trial (NCT01972217) evaluating the combination of olaparib + abiraterone in patients with mCRPC did not detect any clinically relevant drug-drug interactions between olaparib and abiraterone. However, the sample size was small and interpatient variability was large [6]. Therefore, PK analyses for patients in PROpel will help to determine whether any drug-drug interactions occur when olaparib and abiraterone are combined at their full monotherapy doses.

The study design, eligibility criteria, methods, and patient disposition for PROpel have previously been published [1]. In brief, patients were randomized 1:1 to receive either olaparib (full monotherapy dose of 300 mg twice daily) or placebo, with standard-dose abiraterone (1000 mg once daily) plus prednisone/prednisolone (5 mg twice daily). Prior treatment with chemotherapy or next-generation hormonal agents (NHAs) for first-line mCRPC was not permitted.

At selected sites, PK analysis was performed for a subset of patients (≥50 per treatment arm) after they provided informed consent. Patient blood samples were collected at steady state (visit 4) before and at several time points after dose administration (0.5 ± 0.25 h, 2 ± 0.5 h, 3 ± 0.5 h, 5 ± 0.5 h, and 8 ± 1 h after drug administration). Patients were required to fast for at least 2 h before and for 1 h after each dose of abiraterone and, for PK blood sampling, for 1 h before and 2 h after taking the olaparib dose. All blood samples were collected in tubes containing K_2EDTA anticoagulant. For abiraterone and Δ^4-abiraterone analysis, sample collection and processing occurred on ice, and all blood samples were frozen at −70°C within 30 min of plasma preparation. Olaparib, abiraterone, and Δ^4-abiraterone concentrations were determined via liquid chromatography mass spectrometry using deuterated internal standards. The lower limit of quantification for olaparib was 20 ng/ml. The calibration curve range was 1–500 ng/ml for abiraterone and 0.1–20 ng/ml for Δ^4-abiraterone [7].

Table 1 – Olaparib steady-state PK parameters in PROpel and phase 3 olaparib monotherapy studies

Parameter	Ovarian cancer		Breast cancer		Prostate cancer		
	SOLO2 PPK [9] (*N* = 91)	SOLO3 PPK (*N* = 80)	OlympiA PPK (*N* = 69)	OlympiAD PPK (*N* = 36)	PROfound PPK (*N* = 72)	PROfound NCA (*N* = 65)	PROpel NCA (*N* = 66)
$C_{max,ss}$ (μg/ml)							
Gmean (GCV%)	6.83 (32.5)	7.62 (24.7)	6.18 (29.2)	6.48 (40.2)	7.33 (29.9)	7.51 (33.6)	6.28 (33.7)
AUC_{0-12} (μg.h/mL)							
Gmean (GCV%)	41.4 (42.1)	49.8 (34.8)	37.3 (38.7)	42.4 (54.3)	48.4 (44.1)	48.8[a] (46.5)	39.3[b] (42.2)
$C_{min,ss}$ (μg/ml)							
Gmean (GCV%)	1.19 (74.6)	1.62 (69.5)	1.06 (65.5)	1.38 (97.1)	1.61 (82.7)	1.64[a] (87.1)	1.01[b] (86.1)
Median weight, kg	71.0	65.0	66.0	62.0	77.0	78.5	82.5
(range)	(45–150)	(44–124)	(43–145)	(42–113)	(45–119)	(45–119)	(60–182)

AUC_{ss} = steady-state area under the plasma concentration curve; $C_{max,ss}$ = maximum plasma concentrations at steady state; $C_{min,ss}$ = minimum plasma concentrations at steady state; Gmean = geometric mean; GCV = geometric coefficient of variation; NCA = noncompartmental analysis; PK = pharmacokinetic; PPK = PK population analysis.

n = N for all other parameters unless stated otherwise.

[a] *n* = 30 for this analysis.

[b] *n* = 52 for this parameter.

Noncompartmental analysis was performed to obtain PK parameters (area under the plasma concentration curve [AUC] and maximum and minimum plasma concentrations [C_{max} and C_{min}]) to evaluate the effect of olaparib on abiraterone PK. Olaparib PK parameters in the PROpel trial were compared with data from monotherapy trials to evaluate the effect of abiraterone on olaparib.

The PROpel PK subset included 66 patients from the olaparib + abiraterone arm and 58 patients from the placebo + abiraterone arm. Baseline characteristics were generally well balanced between treatment arms and similar to the overall PROpel population (Supplementary Table 1).

Olaparib absorption was rapid at steady state, with a median time to maximum plasma concentration at steady state ($t_{max,ss}$) of 2 h. Table 1 presents steady-state C_{max}, C_{min}, and AUC results for olaparib when administered in combination with abiraterone. These steady-state exposures in PROpel were comparable with those reported in olaparib monotherapy trials, indicating that combination with abiraterone did not impact the olaparib PK parameters.

There was no apparent correlation between olaparib steady-state exposures and patient median baseline weight across olaparib monotherapy trials and PROpel, suggesting that weight did not impact olaparib PK activity (Table 1). Interpatient variability for olaparib PK parameters in PROpel and olaparib monotherapy trials was moderate (25–40%) to high (>40%; Table 1 and Supplementary Fig. 1).

For abiraterone and Δ^4-abiraterone, $t_{max,ss}$ was rapid in both treatment arms (Table 2). The steady-state exposures for abiraterone ($C_{max,ss}$, $C_{min,ss}$ and AUC) were similar between treatment arms (Table 2) and to those reported for monotherapy trials (Supplementary Table 2). For Δ^4-abiraterone, steady-state exposures were slightly lower when abiraterone was administered with olaparib than with placebo (Table 2). There was high interpatient variability (>40%) for all steady-state exposure parameters in the PROpel PK population for abiraterone and Δ^4-abiraterone (Table 2 and Supplementary Fig. 2). These data suggest that olaparib did not impact known variability in PK parameters for abiraterone, and while there were slight reductions in steady-state exposures for Δ^4-abiraterone, the clinical significance is unclear considering the high interpatient variability and questions over the clinical importance of Δ^4-abiraterone for mCRPC.

PK analysis for the phase 3 PROpel trial demonstrates that there were no clinically relevant drug-drug interactions between olaparib and abiraterone when given in combination. As with phase 2 NCT01972217, interpatient variability was high for abiraterone in the PROpel PK population [6]. As high interpatient variability is an intrinsic factor of abiraterone, these results were not unexpected and olaparib did not impact this known variability [8]. The presence of moderate to high interpatient variability for olaparib across the monotherapy and PROpel studies also suggests that this variability is an intrinsic characteristic of olaparib PK.

A limitation of this analysis is that the monotherapy trials used for comparison of olaparib PK parameters had different patient populations (eg, different cancer types, female patient populations, or a later stage of mCRPC), which may have an unknown effect on the comparison of PK outcomes, although previous population PK modeling indicated that tumor type and sex have a minimal impact on olaparib PK [9]. These results also represent a one-day snapshot of patient steady-state exposures. As factors such as nutrition, hormonal changes, and coexisting disorders can affect drug metabolism, steady-state exposures for individual patients may naturally fluctuate over time. In addition, the present study was not powered to address any associations between olaparib or abiraterone PK parameters and clinical outcomes.

In contrast to other studies combining a PARP inhibitor (PARPi) and an NHA, in PROpel, both olaparib and abiraterone were administered at full monotherapy doses without a clinically significant effect on their PK profiles. In the phase 1b BEDIVERE trial (NCT02924766), dose-limiting toxicities led to cessation of further evaluation of the niraparib + apalutamide combination and a reduction in the niraparib dose when combined with abiraterone [10]. Consequently, in the phase 3 MAGNITUDE trial (NCT03748641), a lower niraparib dose than in phase 2 monotherapy trials was used when it was combined with

Table 2 – Abiraterone and Δ^4-abiraterone steady-state PK parameters in PROpel

Parameter	Abiraterone		Δ4-Abiraterone	
	Placebo bid + Abi	Olaparib 300 mg bid + Abi	Placebo bid + Abi	Olaparib 300 mg bid + Abi
$t_{max,ss}$ (h)				
n	56	64	58	65
Median (range)	2.00 (0.00–8.00)	2.04 (0.00–8.00)	2.01 (0.00–7.00)	2.58 (0.00–8.00)
$C_{max,ss}$ (ng/ml)				
n	56	64	58	65
Gmean (GCV%)	105.4 (105.6)	112.6 (136.9)	3.90 (100.3)	3.02 (101.8)
AUC_{0-8} (ng.h/mL)				
n	44	54	44	54
Gmean (GCV%)	339.5 (78.0)	393.7 (107.5)	14.7 (71.0)	11.7 (80.3)
$C_{min,ss}$ (ng/ml)				
n	44	54	44	54
Gmean (GCV%)	8.5 (95.1)	7.7 (92.4)	0.709 (68.0)	0.491 (79.4)

n = number of patients with data available; Abi = abiraterone 1000 mg once a day; AUC_{0-8} = area under the plasma concentration-time curve from 0 to 8 h after dose; bid = twice a day; $C_{max,ss}$ = maximum plasma concentration at steady state; $C_{min,ss}$ = minimum plasma concentration at steady state; GCV = geometric coefficient of variation; Gmean = geometric mean; PK = pharmacokinetic; $t_{max,ss}$ = median time to maximum plasma concentration at steady state.

abiraterone [11,12]. Similarly, a lower dose of talazoparib was used when combined with enzalutamide in the phase 3 TALAPRO-2 trial (NCT03395197) following higher incidence of safety events when the monotherapy dose was used. This higher incidence might be because of the enzyme-inducing effect of enzalutamide, which could potentially increase the talazoparib exposure by approximately twofold [13–15]. Findings from these early-phase studies highlight the importance of not interchanging PARPi + NHA agents beyond the study protocols used in the phase 3 trials.

It is also important to highlight that across PROpel, MAGNITUDE, and TALAPRO-2 there were drug-drug interaction and safety differences that need to be considered for the different PARPi + NHA combinations, and although increases in the incidence of safety events may occur, these are generally in line with those expected for the individual drugs [1,12,16]. A comparison of efficacy and safety data across the three trials was recently published in a quantitative synthesis and meta-analysis [17].

In conclusion, the favorable PK profile of olaparib when combined with abiraterone observed in PROpel, which is consistent with phase 2 NCT01972217, supports administration of full monotherapy doses of both drugs, offering the opportunity for optimum efficacy and safety.

These data were previously presented in poster format at the American Society of Clinical Oncology 2022 annual meeting on June 3–7, 2022.

Author contributions: Andrew J. Armstrong 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: Armstrong, Clarke, Oya, Saad.
Acquisition of data: All authors.
Analysis and interpretation of data: Armstrong, Zhou, Barker, Dujka.
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Critical revision of the manuscript for important intellectual content: All authors.
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Appendix A. Supplementary data

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