European Journal of Cancer 194 (2023) 113346

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Pharmacokinetic boosting of olaparib: A randomised, cross-over study (PROACTIVE-study)

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Received 3 August 2023; Received in revised form 7 September 2023; Accepted 9 September 2023
Available online 19 September 2023

KEYWORDS
Olaparib;
Pharmacokinetic boosting;
Pharmacoenhancement;
CYP3A4;
Cobicistat

Abstract ***Background:*** Pharmacokinetic (PK) boosting is the intentional use of a drug-drug interaction to enhance systemic drug exposure. PK boosting of olaparib, a CYP3A-substrate, has the potential to reduce PK variability and financial burden. The aim of this study was to investigate equivalence of a boosted, reduced dose of olaparib compared to the non-boosted standard dose. ***Methods:*** This cross-over, multicentre trial compared olaparib 300 mg twice daily (BID) with olaparib 100 mg BID boosted with the strong CYP3A-inhibitor cobicistat 150 mg BID. Patients were randomised to the standard therapy followed by the boosted therapy, or vice

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https://doi.org/10.1016/j.ejca.2023.113346

versa. After seven days of each therapy, dense PK sampling was performed for non-compartmental PK analysis. Equivalence was defined as a 90% Confidence Interval (CI) of the geometric mean ratio (GMR) of the boosted versus standard therapy area under the plasma concentration-time curve ($AUC_{0–12\ h}$) within no-effect boundaries. These boundaries were set at 0.57–1.25, based on previous pharmacokinetic studies with olaparib capsules and tablets.
Results: Of 15 included patients, 12 were eligible for PK analysis. The GMR of the $AUC_{0–12\ h}$ was 1.45 (90% CI 1.27–1.65). No grade ≥3 adverse events were reported during the study.
Conclusions: Boosting a 100 mg BID olaparib dose with cobicistat increases olaparib exposure 1.45-fold, compared to the standard dose of 300 mg BID. Equivalence of the boosted olaparib was thus not established. Boosting remains a promising strategy to reduce the olaparib dose as cobicistat increases olaparib exposure Adequate tolerability of the boosted therapy with higher exposure should be established.

1. Introduction

Olaparib is a potent poly (ADP-ribose) polymerase (PARP) inhibitor approved for the treatment of subtypes of ovarian, breast, pancreatic and prostate cancer [1]. It is an effective treatment, especially in patients with homologous recombination deficient tumours, such as Breast Cancer (BRCA)1- and BRCA2-mutated tumours [2]. Currently, multiple clinical trials are ongoing to broaden its application to new indications and combination therapies [3]. Considering the high costs of olaparib and the expected growing treatment population, strategies to mitigate therapy costs are warranted.

Olaparib tablets are used at a fixed starting dose of 300 mg twice daily (BID) [2]. It is extensively metabolised by the cytochrome P450 3A iso-enzymes (CYP3A) [4]. These enzymes influence the absorption (i.e. bioavailability) and metabolism (i.e. clearance) of olaparib. Variable CYP3A-activity is presumed to be the main cause of the large inter-patient variability in the systemic exposure of olaparib [5,6].

Pharmacokinetic (PK) boosting is the intentional use of a strong inhibitor of a metabolic enzyme, together with a therapeutic drug that is metabolised by the same enzyme, to increase drug exposure [7]. Boosting increases the bioavailability and reduces the clearance of the therapeutic drug, which may lead to higher drug exposure. The concept of PK boosting is used extensively outside the oncology field in millions of people living with human immunodeficiency virus (HIV).[7] Recently, it has gained more interest in oncology as it may also facilitate lower doses and oral use of drugs with a low bioavailability [8,9].

PK boosting of olaparib is believed to be promising as it could reduce the inter-patient variability in exposure by blocking CYP3A [7]. Predictable olaparib exposure may reduce the number of patients who are unintentionally under- or overtreated. Furthermore, olaparib is expensive and administering a reduced boosted dose will lead to substantial cost reductions. A reduced dose of olaparib can be boosted by coadministration with cobicistat, a non-therapeutic, strong CYP3A-inhibitor [10]. However, it is currently unknown what the effect of cobicistat is on olaparib exposure. The aim of this study was to develop a dosing strategy for olaparib by determining the effect of PK boosting on a reduced dose of olaparib compared to the standard dose.

2. Patients and methods

2.1. Study design

This randomised, cross-over, open-label, drug-drug interaction study compared the PK of olaparib at the standard monotherapy dose of 300 mg BID with the boosted combination of olaparib 100 mg BID and cobicistat 150 mg BID. The dose of 100 mg in combination with cobicistat was based on the drug label, where a 3-fold dose reduction is recommended when olaparib is combined with a strong CYP3A-inhibitor [1]. This study (NCT05078671) was approved by the medical ethics committee 'METC Oost-Nederland' and conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. All patients gave written informed consent before entering the study.

After inclusion, patients were randomised for PK assessment of the standard therapy followed by the boosted therapy, or vice versa, as depicted in Fig. 1. Based on the elimination half-life of olaparib of approximately 15 hours, steady-state PK was reached after approximately 3.5 days of treatment [1]. As the elimination half-life of olaparib might be prolonged in presence of the booster, the evaluation was performed after seven days of treatment. After PK assessment, patients switched to the other therapy for the following seven days. After trial termination, patients gave their preference on a 7-point Likert scale and returned to the standard dose of olaparib. Adverse events and laboratory safety were monitored and graded using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 [11].

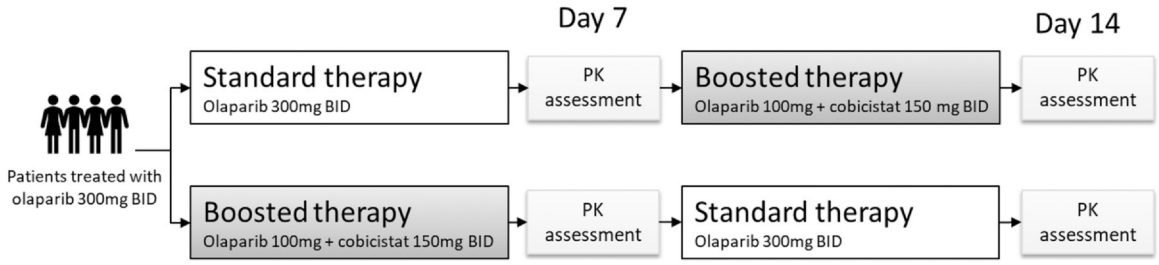

Fig. 1. Overview of study design.

2.2. Patient selection

Patients were enroled at three investigational sites in the Netherlands (Erasmus Medical Centre, Rotterdam; the Netherlands Cancer Institute, Amsterdam; Radboud University Medical Centre, Nijmegen). Eligible patients were already on treatment with or starting treatment with olaparib 300 mg BID according to the drug label and physician's discretion and were ≥18 years old. Patients had an Eastern Cooperative Oncology Group (ECOG) performance status of zero or one and an estimated glomerular filtration rate of ≥50 ml/min. The use of other potent CYP3A-inhibitors or -inducers, that could interfere with the PK of olaparib, was prohibited. Changes in co-medication were recorded during the study. Patients who dropped-out before the second PK assessment were ineligible for the analyses of the primary endpoint and were therefore replaced by a new patient.

2.3. Pharmacokinetic assessment

Dense PK assessment was performed on day 7 and 14. Patients were hospitalised and study medication was taken after overnight fasting. Food intake was allowed 1 hour after olaparib intake. Blood samples were taken in K2-EDTA containing tubes at the following timepoints: pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 hours post-dose. Olaparib plasma concentrations were measured using cross-validated liquid chromatography tandem mass-spectrometry at the three sites [12,13]. The maximal deviation in measured concentrations was 10.6%, 9.3%, 7.8% for quality control samples of 0.583, 2.00 and 5.000 µg/ml respectively. The limits of quantification for olaparib of the three assays used in this study were 0.20–20.00 µg/ml, 0.005–10.00 µg/ml and 0.10–10.00 µg/ml, respectively.

2.4. Statistical analysis

The primary aim of this study was PK equivalency of the area under the plasma concentration-time curve over one dosing interval ($AUC_{0-12\,h}$) for the standard monotherapy compared to the boosted therapy. PK equivalence was established if 90% Confidence Interval (CI) of the geometric mean ratio (GMR) of the $AUC_{0-12\,h}$ of olaparib with the boosted therapy compared to the standard therapy were within the no-effect boundaries of 0.57–1.25 (= 0.8 capsule formulation–1.25 tablet formulation). These no-effect boundaries were based on the standard bio-equivalence margins of 0.8–1.25. The lower boundary was broadened based on the lower exposure observed with use of olaparib capsules, which was the formulation that was used for the pivotal registration trials and evaluated for treatment efficacy (Eq. 1) [6,14]. Secondary endpoints were the observed maximum plasma concentration (C_{max}) and trough plasma concentration (C_{trough}), inter-patient variability and adverse events.

$$\begin{aligned} Lower\ \ margin &= standard\ \ equivalence\ \ margin \\ &\quad * \frac{Geometric\ \ mean\ \ AUC\ \ capsules}{Geometric\ \ mean\ \ AUC\ \ tablets} \\ &= 0.8 \cdot \frac{41.5}{58.4} = 0.57 \end{aligned} \tag{1}$$

For the power calculation, the intra-patient variability of olaparib exposure was assumed to be half the size of the reported inter-patient variability of 44% [15]. With a coefficient of variation (CV) for multiplicative testing within the patient (i.e. intra-patient variability) of 22%, a sample size of 18 patients was required to show equivalence with a power of 90% and a two-sided significance level of 0.05.

Based on the higher olaparib concentrations measured with the boosted therapy, an interim analysis was performed after inclusion of twelve evaluable patients. The aim was to establish whether the primary objective of PK equivalency was still feasible. A sensitivity analysis was performed to determine if the inclusion of six more patients could affect the outcome. It was assumed that the next six patients would have the perfect ratio of 1.00 between the two therapies, which reflects absolute PK equivalency. If inclusion of six more patients would not affect the outcome, enrolment was closed.

Steady state PK parameters were determined with standard, non-compartmental analysis. The $AUC_{0-12\,h}$ was calculated using the linear-up log-down method. C_{max} was defined as the highest observed concentration, C_{trough} was defined as the measured concentration 12 hours after intake. Initial half-life was derived based on samples collected until twelve hours after intake. PK

Table 1
Baseline characteristics of the evaluable patients.

Total	N = 12
Age (years) [range]	63 [55–78]
Gender	
Female	7 (58%)
Male	5 (42%)
BMI (kg/m^2) [range]	23 [21–34]
Ethnicity	
Caucasian/White	12 (100%)
ECOG Performance status	
0	9 (75%)
1	3 (25%)
Tumour type	
Breast	1 (8%)
Ovarian	6 (50%)
Pancreas	1 (8%)
Prostate	4 (33%)
Months on olaparib therapy [range]	19 [1–125]
BRCAm	
BRCA1m	3 (25%)
BRCA2m	6 (50%)
No	2 (17%)
Unknown	1 (8%)
eGFR (ml/min) [range]	75 [53 – 113]

BMI, body mass index; BRCAm, Breast Cancer gene mutational status; ECOG, Eastern Cooperative Oncology Group; eGFR, estimated glomerular filtration rate.

parameters were log-transformed for further analyses [16]. Analyses were performed in R version 4.1.3 (R-project, Vienna Austria) using the validated R-package 'NonCompart' [17].

3. Results

3.1. Patients

Between February 2022 and January 2023, 15 patients were enroled in the study. Patients were already on olaparib treatment for a median period of 19 months (range 1–124 months). Three patients did not complete the study due to illness (n = 1 headache, n = 1 fatigue) or disease progression (n = 1). Baseline characteristics of the twelve evaluable patients are depicted in Table 1.

3.2. Pharmacokinetics

Out of 263 collected samples, 260 samples were used in the PK analyses (n = 2 excluded at T = 12 hours due to erroneousness intake of olaparib before sample collection, n = 1 excluded at T = 3 hours due to delay in sample collections and therefore overlap with T = 4 hours collection). All measured concentrations were within the limits of quantification.

The observed pharmacokinetics are depicted in Fig. 2A and Table 2. The geometric mean of the olaparib $AUC_{0–12\,h}$ was 29.4 µg*h/ml (95% CI 22.2–38.9, CV 46%) for the standard therapy, compared to 42.7 µg*h/ml (95% CI 33.2–55.1, CV 41%) for the boosted therapy. This resulted in a GMR of the $AUC_{0–12\,h}$ of the boosted compared to the standard therapy of 1.45 (90% CI 1.27–1.65) (Fig. 2B). Initial half-life with the standard therapy was 2.79 hours (95% CI 2.38–3.26) compared to 5.67 hours (95% CI 4.14–7.83) with the boosted therapy, indicating that time to reach steady state pharmacokinetics was doubled under the boosted regimen form approximately 3.5 days to 7 days. Individual PK curves are provided in Supplementary Fig. S1.

The sensitivity analysis, simulating that the following six patients would have the perfect equivalent $AUC_{0–12\,h}$ ratio of 1.00 between the two therapies, resulted in a GMR of the $AUC_{0–12\,h}$ of 1.06 (90% CI 0.87–1.30). This was still outside the predefined no-effect boundaries for PK equivalency (Fig. 2B). The primary outcome of the study would not change with the inclusion of six more

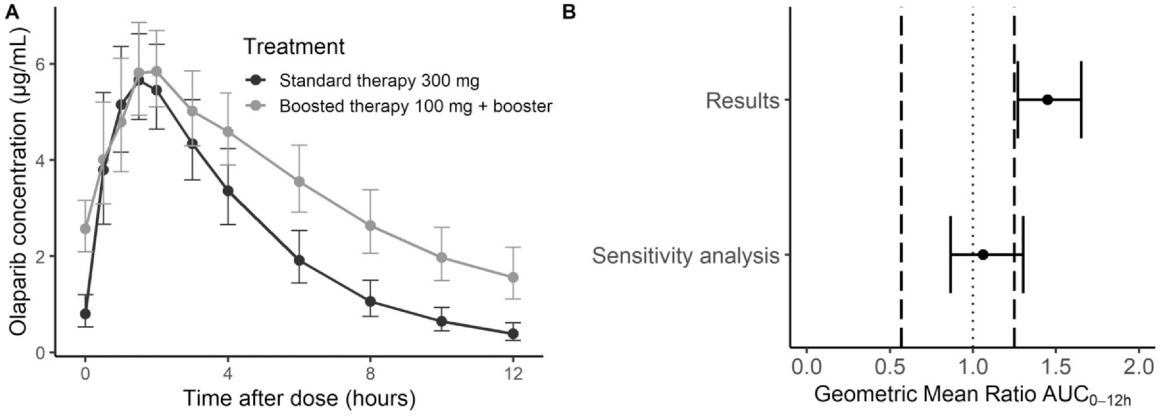

Fig. 2. (A) Concentration-time curve of olaparib standard monotherapy and boosted therapy. (B) Geometric mean ratio and corresponding 90% confidence interval of $AUC_{0–12\,h}$ of the boosted therapy versus the standard therapy of the results of 12 evaluable patients and of the sensitivity analysis. Vertical dashed lines represent the predefined no-effect boundaries of 0.57 and 1.25, vertical dotted line represents the equivalent ratio of 1.00. $AUC_{0–12\,h}$, area under the plasma concentration-time curve over one dosing interval.

Table 2
Pharmacokinetic parameters at steady state of olaparib of the standard monotherapy and boosted therapy.

	Standard therapy (CV%) [95% CI]	Boosted therapy (CV%) [95% CI]	Geometric mean ratio [90% CI]
$AUC_{0-12\,h}$ (μg*h/ml)	29.4 (46%) [22.2–38.9]	42.7 (41%) [33.2–55.1]	1.45 [1.27–1.65]
C_{max} (μg/ml)	6.37 (37%) [5.07–8.00]	6.19 (28%) [5.19–7.39]	0.97 [0.84–1.12]
T_{max} (h)	1.25 (66%) [0.85–1.83]	1.67 (42%) [1.30–2.16]	1.34 [1.03–1.75]
C_{trough} (μg/ml)	0.39 (107%) [0.21–0.73]	1.56 (77%) [0.99–2.46]	4.14 [3.25–5.27]

$AUC_{0-12\,h}$, area under the plasma concentration-time curve over one dosing interval; CI, confidence interval; C_{max}, maximum plasma concentration; C_{trough}, trough plasma concentration; CV, coefficient of variation; T_{max}, time of maximum plasma concentration.

Table 3
Reported adverse events at baseline, during olaparib standard and the boosted therapy, according to CTCAE version 5.0.

	Baseline	Standard therapy	Boosted therapy
Grade 1–2 AE	22	19	25
Anaemia	1	2	1
Anorexia	1	1	1
Arthralgia	1	1	0
Back pain	3	1	2
Blood bilirubin increased	0	0	1
Bruising	1	1	1
Constipation	1	0	0
Creatinine increased	0	0	2
Depression	0	1	0
Diarrhoea	1	1	1
Dysgeusia	1	1	1
Dry mouth	1	1	0
Oedema limbs	0	0	1
Fatigue	2	1	2
Gastroesophageal reflux disease	0	0	1
Nausea	2	1	2
Neutrophil count decreased	0	1	1
Peripheral sensory neuropathy	4	3	4
Platelet count decreased	1	0	1
Pruritis	0	0	1
Rash	1	1	1
White blood cell decreased	1	2	1
Grade ≥3 AE	0	0	0
Number of patients with any AE	6	5	7

AE, adverse event; CTCAE, common terminology criteria for adverse events.

patients. Therefore, the study was closed after inclusion of twelve evaluable patients.

3.3. Safety and patient preference

Only grade 1 or 2 adverse events were reported (Table 3). As almost all patients were already treated with olaparib, adverse events at baseline were most likely related to olaparib standard therapy or to previous systemic treatment. No patients experienced grade ≥3 adverse events. No relevant changes in adverse events were seen with the boosted therapy during the 7-day study period.

Overall, patients did not have a clear preference for any treatment with a mean score of 4.5 (range 1–7) on a 7-point Likert scale, where one was a strong preference for the standard therapy and seven was a strong preference for the boosted therapy.

4. Discussion

This study did not show equivalence of a boosted, reduced dose of olaparib in comparison to the standard dose on steady-state pharmacokinetics. Although the 3-fold dose reduction of olaparib used in this study was in line with the drug label recommendations for combining olaparib with a strong CYP3A-inhibitor, boosting still resulted in a 45% increase in exposure compared to standard dose. Despite this increase in exposure, no increase in adverse events was observed in this short-term study period. The C_{max} was similar between both treatments, whilst C_{trough} markedly increased with the boosted therapy, suggesting a large impact of CYP3A-inhibition on both the bioavailability and clearance of olaparib. Based on the increased olaparib exposure in all twelve patients, boosting will certainly not lead to underexposure.

Pooled data of phase I, II and III studies of olaparib found a geometric mean $AUC_{0-12\,h}$ of 49.0 μg*h/ml (CV 52%, range 16.5–183) in 277 patients treated with the standard dose, which is approximately 67% higher than in our study [18]. The relatively low exposure in our study population may be due to the selection of patients who tolerated the standard dose of 300 mg BID well for relatively longer periods, whereas patients who already had dose reductions were excluded upfront. The side effects of olaparib are related to systemic exposure and due to these side effects, 16–28% of patients require a dose reduction in the first months of treatment [19–25]. The majority of patients was included after several months of olaparib treatment. This could have led to selected inclusion of patients who did not require dose reductions due to few side effects and lower systemic exposure. Interestingly, although a low exposure at the standard dose was observed, the boosted therapy resulted in an exposure ($AUC_{0-12\,h}$ 42.7 μg*h/ml, CV 41%, range 24.7–83.7) similar to previously reported under standard dosing.

Concomitant intake of olaparib with the strong CYP3A-inhibitor cobicistat led to a larger increase in exposure than anticipated. A drug-drug interaction study by Dirix et al. showed that the strong CYP3A-inhibitor itraconazole increased the olaparib AUC with 2.70-fold (90% CI 2.44–2.97) [4]. Corrected for the olaparib dose reduction, cobicistat increased olaparib exposure approximately 4.4-fold in our study. This difference might be caused by a stronger CYP3A-inhibition with cobicistat compared to

itraconazole [26]. Itraconazole is a reversible CYP3A-inhibitor, while cobicistat is a mechanism-based inhibitor, which binds irreversibly to CYP3A. CYP3A-activity will only recover after production of new CYP3A-enzymes [26,27]. Moreover, cobicistat is also known to inhibit CYP2D6 and transporters P-gp, BRCP, MATE1, OATP1B1 and OATP1B3, whilst itraconazole inhibits P-gp and to less extent CYP2D6 besides CYP3A4, which might also contribute to the different interaction potential [28–30]. Another possible explanation is that our study population shows a larger effect of CYP3A-inhibtion due to a higher CYP3A-activity. A more active CYP3A-phenotype can also explain the low olaparib exposure at the standard dose. Theoretically, these patients have a more pronounced effect of CYP3A-inhibition due to increased activity of the enzyme, which could explain the larger increase in olaparib exposure by CYP3A-inhibition. Of note, we did not observe an increase in adverse events despite the increase exposure.

To the best of our knowledge, this is the first study exploring the possibility for PK boosting of a PARP-inhibitor. In oncology, PK boosting is gaining interest. Previous studies have shown that boosting of a lower dose of erlotinib and ibrutinib is feasible and results in similar exposure levels, and reduces inter-patient variability of ibrutinib exposure [31,32]. Furthermore, boosting has been applied to increase exposure in individual patients with subtherapeutic drug concentrations [33–37]. Our results add to this rapidly expanding field of anticancer drug boosting as we show that the concept of PK boosting can also be used for olaparib.

A limitation of our study is the potential selection of patients with a low olaparib exposure at the standard dose. As hypothesised, patients with a more active CYP3A-phenotype might have been selected. Patients with a less active phenotype might have a smaller effect of CYP3A-inhibition and this hypothesis requires further study. Our hypothesis is that boosting will reduce inter-patient variability in exposure. This was shown with marginally lower CVs of the PK parameters with the boosted therapy in our small group of patients and needs to be confirmed in a larger patient group. Less inter-patient pharmacokinetic variability will put less patients at risk for over- or undertreatment. Olaparib has no exposure-response relation for efficacy at the recommended dose, therefore, there is little risk for undertreatment [19,38]. However, olaparib does have an exposure-toxicity relation [19]. If all patients show the 1.45-fold increase in olaparib exposure, PK boosting could decrease tolerability. If the 1.45-fold increase in our study population is caused by the high CYP3A-activity, as explained earlier, an unselected patient population might not show this increase in exposure. In the latter scenario, the reduction in inter-patient variability could improve tolerability, as less patients are overtreated.

Another limitation of our study is the relatively short exposure period to the boosted treatment, whereby only immediate onset toxicity could be monitored. During the study period of seven days the boosted treatment was well-tolerated. However, haematological and gastro-intestinal adverse events occur up until three months after start of olaparib [24]. Although olaparib toxicity is considered manageable, the long-term tolerability should be established before the boosted therapy can be implemented in routine care [24].

As this is an academia-driven study, uptake of the boosted dosing regimen in the olaparib drug label is unlikely. Even after long-term tolerability has been established, the boosted dosing regimen of olaparib will remain off-label use. Off-label use of anticancer drugs is relatively common and can be implemented in routine care if substantiated with robust evidence [39,40]. This study was designed to establish equivalent drug exposure as defined by the guidelines of the FDA and EMA [14,41]. Since equivalence was not established and lower dosages are not feasible with the current olaparib formulations, robust evidence on the efficacy and tolerability should be collected before implementation.

Olaparib is an expensive drug and PK boosting is a promising tool to reduce financial toxicity and impact on the healthcare budget. The rising costs of anticancer drugs are becoming a global concern and it can cause challenges in treatment access [42]. Olaparib tablets are flat priced at €48.37 per tablet in the Netherlands [43]. At the standard dose, treatment consists of four tablets daily and monthly expenses of nearly €6000 are high. These expenses can be substantially lowered by reducing the olaparib pill burden to two tablets daily with boosting. Cobicistat is relatively inexpensive at €1.09 per tablet in the Netherlands [44]. Therefore, boosting has the potential to reduce the costs of olaparib therapy with nearly 50%. PK boosting could provide one of the solutions for the dilemma of rising costs of anticancer drugs.

5. Conclusions

This is the first study to investigate the PK boosting of a PARP-inhibitor with cobicistat. Boosting 100 mg BID olaparib with the strong CYP3A-inhibitor cobicistat resulted in a 1.45-fold increase in exposure, compared to the standard dose of 300 mg BID. Hence, boosting did not lead to equivalent exposure to olaparib. Boosting of olaparib is nevertheless a promising strategy to reduce the olaparib dose. These results encourage a prospective study of boosted olaparib with toxicity-guided dose reductions.

Funding

This study was funded by ZonMw, The Netherlands Organisation for Health Research and Development, as part of the Goed Gebruik Geneesmiddelen programme (grant number 10140021910005).

CRediT authorship contribution statement

Joanneke Overbeek: Methodology, Formal analysis, Investigation, Writing – original draft, Visualization, Project administration. **Niels Guchelaar**: Formal analysis, Investigation, Writing – original draft, Project administration. **Ma Ida Mohmaed Ali:** Investigation, Writing – original draft, Project administration. **Petronella Ottevanger:** Resources, Writing – review & editing. **Haiko Bloemendal:** Investigation, Writing – review & editing, Supervision. **Stijn Koolen:** Writing – review & editing. **Ron Mathijssen:** Investigation, Writing – review & editing. **Ingrid Boere:** Resources, Writing – review & editing. **Paul Hamberg:** Resources, Writing – review & editing. **Alwin Huitema:** Writing – review & editing. **Gabe Sonke:** Resources, Writing – review & editing. **Frans Opdam:** Investigation, Writing – review & editing. **Rob ter Heine:** Conceptualization, Methodology, Writing – review & editing; Supervision. **Nielka van Erp:** Conceptualization, Methodology, Writing – review & editing; Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: RHJM reports research funding paid to the institute from Astellas, Bayer, Boehringer-Ingelheim, Cristal Therapeutics, Novartis, Pamgene, Pfizer, Roche, Sanofi, and Servier. IB reports research funding paid to the institute from GSK. PH reports personal fees from Astellas and consulting or advisory fees from Astellas, MSD, Pfizer AstraZeneca, BMS, Ipsen. GSS reports research funding paid to the institute from Agendia, AstraZeneca, Merck, Novartis, Roche, and Seagen and a consulting role for Biovica and Seagen. NPvE reports research funding paid to the institute from Astellas, Janssen-Cilag, Ipsen. JKO, NADG, MIMA, PBO, HJB, SLWK, ADRH, FLO and RtH declare no potential conflicts of interest.

Appendix A. Supporting material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2023.113346.

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