

Influence of Enzalutamide on Cabazitaxel Pharmacokinetics: a Drug-Drug Interaction Study in Metastatic Castration-resistant Prostate Cancer (mCRPC) Patients



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Abstract

Purpose: In ongoing clinical research on metastatic castration-resistant prostate cancer (mCRPC) treatment, the potential enhanced efficacy of the combination of taxanes with AR-targeted agents, that is, enzalutamide and abiraterone, is currently being explored. Because enzalutamide induces the CYP3A4 enzyme and taxanes are metabolized by this enzyme, a potential drug-drug interaction needs to be investigated.

Experimental Design: Therefore, we performed a pharmacokinetic cross-over study in mCRPC patients who were scheduled for treatment with cabazitaxel Q3W (25 mg/m²). Patients were studied for three consecutive cabazitaxel cycles. Enzalutamide (160 mg once daily) was administered concomitantly after the first cabazitaxel cycle, during 6 weeks. Primary endpoint was the difference in mean area under the curve (AUC) between the first (cabazitaxel monotherapy) and third cabazitaxel cycle, when enzalutamide was added.

Results: A potential clinically relevant 22% (95% CI, 9%–34%; $P = 0.005$) reduction in cabazitaxel exposure was found with concomitant enzalutamide use. The geometric mean AUC_{0–24h} of cabazitaxel was 181 ng·h/mL (95% CI, 150–219 ng·h/mL) in cycle 3 and 234 ng·h/mL (95% CI, 209–261 ng·h/mL) in cycle 1. This combination did not result in excessive toxicity, whereas PSA response was promising.

Conclusions: We found a significant decrease in cabazitaxel exposure when combined with enzalutamide. In an era of clinical trials on combination strategies for mCRPC, it is important to be aware of clinically relevant drug-drug interactions. Because recent study results support the use of a lower standard cabazitaxel dose of 20 mg/m², the clinical relevance of this interaction may be substantial, because the addition of enzalutamide may result in subtherapeutic cabazitaxel exposure. *Clin Cancer Res*; 24(3); 541–6. ©2017 AACR.

Introduction

The current treatment paradigm in mCRPC comprises monotherapy options with chemotherapy, that is, docetaxel or cabazitaxel, or with novel hormonal therapies, including enzalutamide and abiraterone (1). Clinical studies with various combinations of therapies, for example, taxanes with novel hormonal therapies, with various designs and aims, are in progress (e.g., <https://clinicaltrials.gov/ct2/show/NCT02522715>; refs. 2–5). A summary

of ongoing clinical trials on these combinations was recently reviewed by Sternberg, and showed the rationale for combination therapies (6). In addition, preclinical *in vivo* work has shown that the activity of cabazitaxel is strongly affected by hormonal manipulations, for example, either by castration or testosterone supplementation (7). Clinical studies with combined treatments, although, warrant thorough pharmacokinetic investigation to test for clinical relevant drug-drug interactions.

Taxanes, that is, docetaxel and cabazitaxel, have an extensive hepatic metabolism (63–77%) and biliary excretion (8). Their metabolism is mediated by CYP3A iso-enzymes in the liver, and for a small part by CYP2C8. Therefore, liver (dys-)function is a major factor in taxane dose adaptations (9). Pharmacokinetics of docetaxel show a considerable interpatient variability (30–50%), depending on patient characteristics, like gender and age. The interpatient variability of cabazitaxel is moderate (24%) and cabazitaxel pharmacokinetics are less susceptible for patient characteristics (10). However, the use of co-medication and herbal supplements, especially (strong) inducers/inhibitors of the CYP3A-system influence the pharmacokinetics of all taxanes (11–13). The influence of CYP3A-inducers on the pharmacokinetics of cabazitaxel have been extensively investigated by Sarantopoulos and colleagues, showing that cabazitaxel is susceptible for CYP3A induction or inhibition. Repeated administration of a strong CYP3A inducer, rifampin, resulted in an 21% increase

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Translational Relevance

Preclinical data suggest enhanced efficacy of cabazitaxel when combined with hormonal therapies for metastatic castration-resistant prostate cancer (mCRPC). Clinical studies on combining taxanes, i.e., docetaxel and cabazitaxel, and AR-targeted agents, that is, enzalutamide and abiraterone, are ongoing. It is important to be aware of potential drug–drug interactions between these agents, especially since enzalutamide is known to be a strong CYP3A4 inducer and taxanes are metabolized by this enzyme. We performed a pharmacokinetic study to identify the influence of enzalutamide on cabazitaxel concentrations in mCRPC patients. We found a potential clinically relevant reduction in cabazitaxel concentration (>20%) when combined with enzalutamide. Nonetheless, the combination was safe and well-tolerated. Moreover, PSA response levels were higher than expected in this heavily pretreated patient population. Studies with this drug combination are warranted, but investigators need to be aware of the current findings.

in cabazitaxel clearance and a 17% decrease in cabazitaxel concentration (14). Additionally, the pharmacokinetics of taxanes can potentially be influenced by changes in drug transporters, like ABCB1 (P-glycoprotein; refs. 11, 15). Although cabazitaxel has less propensity for ABCB1 mediated drug resistance, the upregulation of the efflux pump can potentially impact the pharmacokinetics of cabazitaxel (16).

Enzalutamide is known to be a moderate inducer of CYP2C9 and CYP2C19 and a strong inducer of CYP3A4. Maximal CYP3A4 induction by enzalutamide may not appear until one month after treatment start, when steady-state levels of enzalutamide are reached (17). Because enzalutamide induces CYP3A4, and because taxanes are predominantly metabolized via that enzyme, a drug–drug interaction between these agents is expected (12, 15).

Recently, Morris and colleagues published a pharmacokinetic study in patients on the combination of enzalutamide and docetaxel (18). They found a 12% decrease in docetaxel concentrations during concomitant enzalutamide use compared with docetaxel alone, which they regarded as clinically irrelevant. However, given the short combination period of only 3 weeks, during which steady state exposure of enzalutamide may not have been reached yet, the true drug–drug interaction might be larger than reported. The half-life and steady-state level of orally administered enzalutamide (160 mg once daily) are relatively long: 6 days and 4 weeks, respectively. So, to identify the true inductive effects of enzalutamide on cabazitaxel exposure, we aimed to study the combination for at least the time-period that steady state of enzalutamide (i.e., after 4 weeks) is reached (17). Therefore, we studied 3 consecutive cabazitaxel cycles in our trial, where enzalutamide is used for 6 weeks by men with mCRPC.

Patients and Methods

Between April 2015 and August 2016 this prospective, non-randomized, nonblinded, cross-over, pharmacokinetic trial was undertaken in the Erasmus University Medical Center in Rotterdam, the Netherlands. The Ethical board of the Erasmus Univer-

sity Medical Center approved the study protocol and written informed consent was obtained from all participants. The study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki. The study was registered at the Dutch Trial Register (www.trialregister.nl) by number NTR5164.

Study population

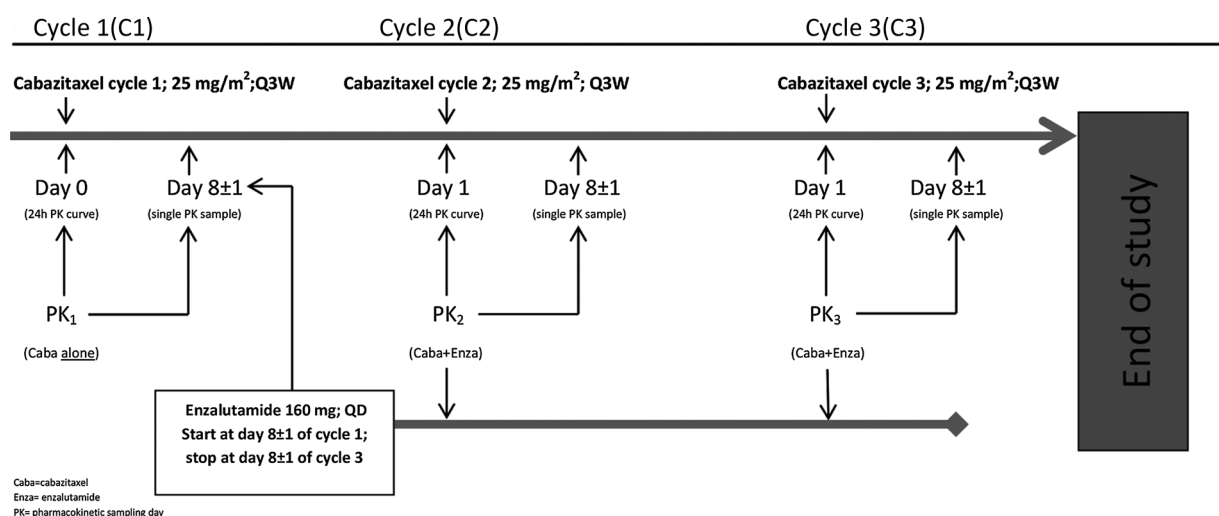
Patients enrolled in this study had histologically proven adenocarcinoma of the prostate with documented progression after docetaxel treatment and were eligible to receive second line chemotherapy, that is, cabazitaxel. As the pharmacokinetic interaction was our primary endpoint, prior cabazitaxel treatment was allowed and prior enzalutamide treatment had to be ceased at least 6 weeks before start of the study. Eligible patients were aged at least 18 years, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and adequate liver function, defined by total bilirubin $\leq 1.5 \times$ the upper limit of normal (ULN; except for documented Gilbert's disease), ASAT and ALAT $\leq 2.5 \times$ ULN (or $\leq 5 \times$ ULN if liver metastases are present). Patients with a medical history of seizures or predisposition to seizures were excluded. Medication or herbal supplements which may interact with either cabazitaxel or enzalutamide, for example, by induction or inhibition of CYP3A4, CYP2C8, CYP2C9, or CYP2C19, were prohibited during this trial.

Study design

Patients received three consecutive cycles of cabazitaxel as a 1-hour infusion of 25 mg/m² once every 3 weeks. Dose modifications of cabazitaxel were allowed to a minimal dose of 12.5 mg/m² (50% of the registered dose). Premedication consisted of intravenously given dexamethasone (10 mg), followed by granisetron 1 mg. Oral prednisone, at a dose of 5 mg twice daily, was taken for as long as cabazitaxel treatment continued. At day 7 after the first cabazitaxel cycle within the study, a daily dose of 160 mg enzalutamide (four capsules of 40 mg, orally) was added until eight (plus/minus one) days after the third cabazitaxel cycle. So, enzalutamide was cotreated for a total of 6 weeks. Enzalutamide administration was at 10.00 AM, without permission of dose interruptions or modifications. Patient compliance was assessed through a patient diary. Using this cross-over design all patients were their own control, making enzalutamide comedication the only structural varying factor. See Fig. 1 for a simplified scheme of the study design.

Pharmacokinetic assessments

Plasma samples for cabazitaxel pharmacokinetic assessments were obtained at cycle 1 (before initiation of enzalutamide dosing), cycle 2 and at cycle 3, when steady state levels of enzalutamide have been reached. Blood samples (4 mL) were withdrawn on the first day of each cabazitaxel cycle, at different time-points (pre-infusion and at 0.5, 0.92, 1.08, 1.25, 1.5, 2, 3, 5, 7, 11–13, 24, and 192 hours after the start of cabazitaxel). Measurement of plasma concentrations of cabazitaxel was performed using a validated liquid chromatography with tandem mass spectrometry methods (UP-MS/MS; refs. 19). We used noncompartmental analysis (Phoenix version 6.1; Pharsight) and estimated the residual AUC by a linear pharmacokinetic curve from the latest measurable pharmacokinetic point. The last pharmacokinetic sample was taken at 192 hours, which corresponds with the regular control at the outpatient clinic at 1 week after cabazitaxel infusion. Pharmacokinetic parameters determined

**Figure 1.**

Study design. The study included three consecutive courses of cabazitaxel, and 1 week after the first cabazitaxel cycle enzalutamide was added for a period of 6 weeks.

included cabazitaxel exposure [expressed as dose-corrected area under the plasma concentration time curves from time zero to infinity ($AUC_{0-\infty}$)]. When cabazitaxel concentrations were below the limit of detection at this point, we used the 24-hour sampling point as latest pharmacokinetic sample, and therefore the dose corrected AUC_{0-24h} as primary outcome measurement. Other pharmacokinetic parameters included were the maximum drug concentration (C_{max}), and its half-life ($t_{1/2}$).

PSA assessments

Although not specified per protocol, serum PSA levels were determined at study baseline and before start of each cycle. Exploratory analyses were performed to identify proportion of patients with $\geq 50\%$ decline of PSA from study start compared to the end of the treatment period.

Statistical analysis

To take into account dose-reduced cabazitaxel cycles, all measured concentrations were dose-corrected to a dose of 25 mg/m² by the formula $AUC^*(25/\text{dose given in that cycle})$. Before analyzing the dose-corrected AUC and maximum cabazitaxel concentrations (C_{max}), a natural log transformation of these data was performed to take into account possible deviations from normality. The (log) dose-corrected AUC of cabazitaxel without enzalutamide (AUC Cycle 1) was compared with the (log) dose-corrected AUC of cabazitaxel with enzalutamide (AUC Cycle 3), using a paired *t*-test. In addition, as a secondary endpoint, the same test was used to compare (log) dose-corrected AUC of cycle 1 to cycle 2, the (log) maximum cabazitaxel concentration (C_{max}) in cycle 1 to cycle 3, and the same for the half-life ($t_{1/2}$) of cabazitaxel. The mean differences and 95% CIs for the differences were exponentiated to provide point estimates of the ratio of geometric means and 95% CIs for these ratios, which can be interpreted as relative differences in percentages. The study required an estimated sample size of 14 evaluable patients to detect a clinical relevant difference in AUC with 80% power and a two-sided significance level of 0.05. IBM SPSS Statistics 21 was used for all analyses.

Results

Patient characteristics and pharmacokinetic parameters

Baseline characteristics are available for all 14 patients and are shown in Table 1. All patients were chemically castrated and used androgen-deprivation therapy throughout the whole study period. Cabazitaxel pharmacokinetic parameters are shown in Table 2. We aimed to identify the $AUC_{0-\infty}$ of cabazitaxel by collecting pharmacokinetic samples up to 192 hours. However, in most cases the concentration of cabazitaxel was below the detection limit (LLQ) in the 192-hour pharmacokinetic samples. As a result the residual AUC was $>20\%$ of the total AUC, which is not acceptable according to the general pharmacokinetic assumptions. Therefore, we had to decide to limit our AUC calculation up to the 24-hour sample (AUC_{0-24h}).

The geometric mean exposure was 22% (95% CI, 9%–34%, $P=0.005$) lower in the third cycle (cabazitaxel combined with

Table 1. Patient characteristics

Characteristic	Value no. (%)
Evaluable patients (n)	14 (100)
Age (years), mean \pm SD	67.7 \pm 6.1
WHO performance status	
0	4 (29)
1	10 (71)
Liver function baseline, mean \pm SD	
Bilirubin ($\mu\text{mol/L}$)	5.4 \pm 2.1
ASAT (U/L)	24.6 \pm 9.9
ALAT (U/L)	19.1 \pm 8.5
Prior therapy	
Docetaxel	14 (100)
Abiraterone	6 (43)
Enzalutamide	3 (21)
Radiotherapy	3 (21)
Experimental ^a	5 (36)
Cabazitaxel	2 (14)
Type of castration	
Chemical	14 (100)

Abbreviations: n, number; WHO, World Health Organization.

^aExperimental included participation in phase I and II clinical trial with a variety of agents: TAS-119, ARN-509, dendritic cell therapy.

Table 2. Cabazitaxel pharmacokinetics

Cabazitaxel PK parameters	C1 (caba)	C2 (caba+enza)	C3 (caba + enza)	Difference C3/C1 % (95% CI)	P ^a
AUC _{0-24h} ; ng*h/mL (CV%)	234 (19)	182 (26)	181 (34)	-22 (-9 till -34)	0.005
C _{max} ; ng/mL (CV%)	138 (39)	96 (49)	96 (20)	-30 (-42 till -16)	0.001
t _{1/2} ; h (CV%)	22 (87)	14 (41)	18 (79)	-18 (-59 till 64)	0.552

Abbreviations: AUC_{0-24h}, area under the curve for 24 hours; C1/2/3, cycle 1/2/3; caba, cabazitaxel; CI, confidence interval, expressed as geometric; C_{max}, maximum concentration, expressed as geometric; CV%, coefficient of variation; enza, enzalutamide; PK, pharmacokinetics; t_{1/2}, half-life, expressed as geometric.

^aComparison between cycle 1 and cycle 3.

enzalutamide: AUC_{0-24h} of 181 ng*h/mL; 95% CI, 150–219 ng*h/mL) compared to the first cycle (cabazitaxel monotherapy: AUC_{0-24h} of 234 ng*h/mL; 95% CI, 209–261 ng*h/mL). Interestingly, this decrease was already observed during cycle 2 (AUC_{0-24h} of 182 ng*h/mL; 95% CI, 157–211 ng*h/mL; relative difference = -22%; 95% CI, -13% to -31%; $P < 0.001$) despite the shorter period of the drug-drug combination during that cycle. In addition, the variation in pharmacokinetic effects, as expressed by the coefficient of variation (CV%), was higher in the third cycle than in cycle 1 and cycle 2 in the study, respectively 34%, 19%, and 26%, see Fig. 2. As secondary endpoints other pharmacokinetic endpoints; maximum concentration (C_{max}) of cabazitaxel and half-life (t_{1/2}) of cabazitaxel were measured, and compared between cycle 1 and cycle 3. The maximum concentration of cabazitaxel in the first cycle (C_{max} 138 ng/mL; 95% CI, 111–171 ng/mL) was significantly higher than in the third cycle (C_{max} 96 ng/mL; 95% CI, 86–108 ng/mL; relative difference, -30%; 95% CI, -42 to -16%; $P = 0.001$). There was no difference in half-life of cabazitaxel between both cycles (cycle 1: t_{1/2} = 22 hours; 95% CI, 14–33 hours vs. cycle 3: t_{1/2} = 18 hours; 95% CI, 12–27 hours; relative difference = -18%; 95% CI, -59% to -64%; $P = 0.552$).

Toxicity and PSA response

There were no unexpected serious adverse events (SAE) during combined treatment with these drugs. A total of four SAEs were generally related to cabazitaxel treatment (monotherapy), including neutropenic fever (two times), deep venous thrombosis, and hypertension. Hypertension (grade 3) occurred during the third cycle, although this patient was already known with hypertension. The deterioration of the blood pressure may be attributed to enzalutamide use as well. Four of six (67%) grade 3–4 adverse

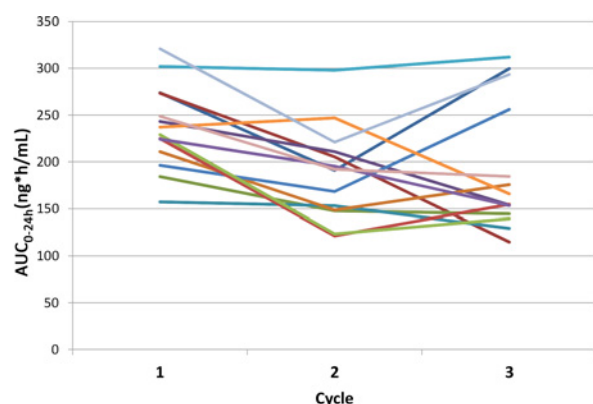
events occurred during cabazitaxel monotherapy, whereas the other two adverse events happened during the combination therapy of cabazitaxel and enzalutamide, indicating an overall well-tolerated combination strategy.

Because PSA response was not specified per protocol, we analyzed response rates in an explorative way. Because baseline PSA was missing for one patient, PSA analyses were performed in 13 of 14 patients. PSA responses of 50% or more were observed in 8 (62%) of the 13 patients at completion of the three consecutive cycles of cabazitaxel in the study, which we regarded as high given the extensive prior treatment in this typical patient cohort (Fig. 3). Five of the PSA responders had prior treatment with an AR-agent, and both cabazitaxel pre-treated patients had a >50% PSA decline.

Discussion

In this pharmacokinetic cross-over study in patients with mCRPC treated with cabazitaxel, we evaluated the difference in exposure (AUC_{0-24h}) of cabazitaxel when administered with or without enzalutamide. Our study showed a significant and potentially clinically important reduction (22%) in cabazitaxel exposure by simultaneous treatment with enzalutamide.

As mentioned, enzalutamide is classified as a strong inducer of CYP3A4 enzyme (17), and all taxanes, including cabazitaxel, are metabolized primarily by this enzyme. Therefore, a drug-drug interaction was expected *a priori*, although the magnitude of that interaction was uncertain. In this study, the inductive effects of enzalutamide on cabazitaxel exposure is relatively high and results in a clinically relevant interaction between these agents. In contrast, Morris and colleagues (18) found a moderate 12% reduction of docetaxel concentration (AUC_{inf}) with concomitant enzalutamide use. The substantial difference between the identified percentages of enzalutamide related drug induction in the study of Morris and colleagues (18) and our cohort may be due to the different taxanes that were used. Although our primary endpoint was to compare cabazitaxel study cycle 1 to cabazitaxel study cycle 3, we already saw comparable geometric cabazitaxel AUC_{0-24h} decreases during cabazitaxel study cycle 2, following 14 days of treatment with enzalutamide. Although the steady state levels of enzalutamide are reached after 4 weeks, the inducing effect on CYP3A4 is probably complete after 2 weeks. This observation is consistent with prior observations that induction of CYP enzymes is complete within 9–14 days after start of treatment with strong CYP inducers (20). Nonetheless, study cycle 3 was not similar to study cycle 2: the interpatient variability was substantially higher in the third cycle, as several patients had higher cabazitaxel concentrations in that cycle than in cycle 2. Contrarily, other patients had a further decrease in cabazitaxel exposure in the third cycle (Fig. 2). The interpatient variability of cabazitaxel is moderate with 24% (10). In this study, it appears that interpatient variability (%CV) increases when cabazitaxel is combined with enzalutamide and even further in consecutive

**Figure 2.**

Individual dose-corrected cabazitaxel AUC_{0-24h}. Each line refers to one patient. The dose-corrected AUC_{0-24h} of cabazitaxel (y-axis) is measured per cycle (x-axis), and AUC values for individual patients are connected between the cycles.

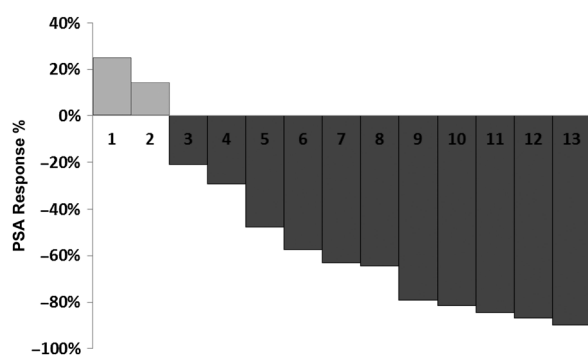


Figure 3.

PSA response after three cycles of cabazitaxel within the study. PSA response is defined as $\geq 50\%$ decline of PSA compared with baseline. $N = 13$, because a baseline PSA value was missing for 1 patient.

cycles. We cannot provide a clear explanation for this phenomenon. This increased variation was not dependent on occurrence of hepatotoxicity, comedication, or number of cabazitaxel cycles preceding the start of this study. Also patient compliance to daily take oral enzalutamide did not differ during the cycles, based on notes in patient diaries. Moreover, medication or herbal supplements that could interact with enzalutamide were prohibited per protocol, so the risk of interpatient variation in pharmacokinetics of enzalutamide, with potential impact on pharmacokinetics of cabazitaxel, is brought back to the minimum. However, enzalutamide concentrations were not measured, which is a limitation of our study.

Recently, the results of the 'PROSELICA' study have become available. PROSELICA was a postmarketing study, mandated by the FDA, to investigate if a 20 mg/m^2 three-weekly dose of cabazitaxel is noninferior to the standard dose of 25 mg/m^2 (21). The PROSELICA study showed a noninferior overall survival outcome with the 20 mg/m^2 dose. As expected the lower dose was also associated with a notably favorable adverse event profile. Although to date the dose in the label has not been changed, in clinical practice the use of the 20 mg/m^2 dose is being adopted widely, both in the United States and in Europe. If indeed such a lower dose of cabazitaxel is applied, an additional reduction of 22% in cabazitaxel exposure by enzalutamide may result in subtherapeutic cabazitaxel concentrations.

Interestingly, the PSA response, which was studied exploratively, was higher in this study than the response rate reported in the TROPIC trial, which was the registration trial for cabazitaxel treatment (62% vs. 39%; refs. 22, 23). The higher PSA response is encouraging, because most of our patients had received prior AR-targeted therapy, several had previously been treated with cabazitaxel, and several had been on clinical phase I and II studies with a variety of drugs, rendering the fourth or even fifth line treatment. Moreover, in our cohort the cabazitaxel concentration was reduced with a mean of 22% for two cycles due to the drug-drug interaction with enzalutamide. This implies that the additive effect of the drug-drug combination on PSA response is promising, despite the inductive effects of enzalutamide on cabazitaxel

pharmacokinetics. Still, our response rates should be interpreted with caution due to the exploratory design of the analysis, the small sample size, and the limited study period.

Furthermore, the combination treatment was very well tolerated considering the low incidence and severity of adverse events, although our results should be seen in perspective given the short treatment period and the prior cabazitaxel cycles that were allowed. In a recent study by Massard and colleagues on the combination of cabazitaxel and abiraterone, also a lower incidence of grade ≥ 3 neutropenia was reported than in the TROPIC trial (56%). This lower incidence of neutropenia did not result in less (marker) efficacy, as PSA levels dropped in 46% patients (4).

In conclusion, our study shows a significant and clinically relevant reduction in cabazitaxel exposure when combined with enzalutamide, most probably due to CYP3A4 induction by enzalutamide. Prospective clinical studies with this promising combination are warranted, but investigators need to be aware of the observed drug-drug interaction.

Disclosure of Potential Conflicts of Interest

B.P.S. Belderbos is a consultant/advisory board member for Astellas. S. Bins reports receiving speakers bureau honoraria from Astellas. P. Hamberg reports receiving speakers bureau honoraria from Cabazitaxel and Enzalutamide. M. Lolkema reports receiving commercial research grants from Astellas, Johnson & Johnson, and Sanofi. R. de Wit is a consultant/advisory board member for Sanofi. R.H.J. Mathijssen reports receiving commercial research grants from and is a consultant/advisory board member for Astellas. No potential conflicts of interest were disclosed by the other authors.

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References

1. Fitzpatrick JM, Bellmunt J, Fizazi K, Heidenreich A, Sternberg CN, Tombal B, et al. Optimal management of metastatic castration-resistant prostate

cancer: highlights from a European Expert Consensus Panel. *Eur J Cancer* 2014;50:1617-27.

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2. Chowdhury S, Davidson R, Coppel A, Mobasheri H, Stari A, Snijder R, et al. The PRESIDE trial: a randomized, double-blind, placebo-controlled Phase 3 efficacy and safety study of continued enzalutamide plus docetaxel after disease progression on enzalutamide alone in patients with metastatic castration-resistant prostate cancer. *J Clin Oncol* 33: 15s, 2015 (suppl; abstr TPS5083).
3. Tagawa ST, Posadas EM, Bruce J, Lim EA, Petrylak DP, Peng W, et al. Phase 1b study of abiraterone acetate plus prednisone and docetaxel in patients with metastatic castration-resistant prostate cancer. *Eur Urol* 2016;70:718–21.
4. Massard C, Mateo J, Lortot Y, Pezaro C, Albiges L, Mehra N, et al. Phase I/II trial of cabazitaxel plus abiraterone in patients with metastatic castration-resistant prostate cancer (mCRPC) progressing after docetaxel and abiraterone. *Ann Oncol* 2017;28:90–5.
5. Kessler ER, Gao D, Flaig TW, Breaker K, Wold M, Wacker M, et al. Phase II study of cabazitaxel with or without abiraterone acetate and prednisone in patients with metastatic castrate resistant prostate cancer after prior docetaxel and abiraterone acetate. *Ann Oncol* 2017;28:668.
6. Sternberg CN. Improving survival for metastatic castrate-resistant prostate cancer: will combination therapy help us to move forward? *Eur Urol* 2016;70:722–3.
7. Mout L, de Ridder C, Stuurman D, Bruijn P, Mathijssen RH, de Wit R, et al. Testosterone abolishes cabazitaxel efficacy in an in vivo model of prostate cancer and affects intratumoral concentrations [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2017; 2017 Apr 1–5; Washington, DC. Philadelphia (PA): AACR; 2017. Abstract nr 1099.
8. Ridoux L, Semiond DR, Vincent C, Fontaine H, Mauriac C, Sanderink GJ, et al. A phase I open-label study investigating the disposition of [¹⁴C]-cabazitaxel in patients with advanced solid tumors. *Anticancer Drugs* 2015;26:350–8.
9. Joerger M. Metabolism of the taxanes including nab-paclitaxel. *Expert Opin Drug Metab Toxicol* 2015;11:691–702.
10. Ferron GM, Dai Y, Semiond D. Population pharmacokinetics of cabazitaxel in patients with advanced solid tumors. *Cancer Chemother Pharmacol* 2013;71:681–92.
11. Nieuweboer AJ, de Morree ES, de Graan AJ, Sparreboom A, de Wit R, Mathijssen RH. Inter-patient variability in docetaxel pharmacokinetics: a review. *Cancer Treat Rev* 2015;41:605–13.
12. Mathijssen RH, Sparreboom A, Verweij J. Determining the optimal dose in the development of anticancer agents. *Nat Rev Clin Oncol* 2014;11:272–81.
13. Janssen A, Verkleij CPM, van der Vlist A, Mathijssen RHJ, Bloemendaal HJ, Ter Heine R. Towards better dose individualisation: metabolic phenotyping to predict cabazitaxel pharmacokinetics in men with prostate cancer. *Br J Cancer* 2017;116:1312–7.
14. Sarantopoulos J, Mita AC, Wade JL, Morris JC, Rixe O, Mita MM, et al. Phase I study of cabazitaxel plus cisplatin in patients with advanced solid tumors: study to evaluate the impact of cytochrome P450 3A inhibitors (aprepitant, ketoconazole) or inducers (rifampin) on the pharmacokinetics of cabazitaxel. *Cancer Chemother Pharmacol* 2014;74:1113–24.
15. Pean E, Demolis P, Moreau A, Hemmings RJ, O'Connor D, Brown D, et al. The European Medicines Agency review of cabazitaxel (Jevtana(R)) for the treatment of hormone-refractory metastatic prostate cancer: summary of the scientific assessment of the committee for medicinal products for human use. *Oncologist* 2012;17:543–9.
16. Bouchet BP, Galmarini CM. Cabazitaxel, a new taxane with favorable properties. *Drugs Today* 2010;46:735–42.
17. Gibbons JA, Ouatas T, Krauwinkel W, Ohtsu Y, van der Walt JS, Beddo V, et al. Clinical pharmacokinetic studies of enzalutamide. *Clin Pharmacokinet* 2015;54:1043–55.
18. Morris MJ, Rathkopf DE, Novotny W, Gibbons JA, Peterson AC, Khondker Z, et al. Phase Ib study of enzalutamide in combination with docetaxel in men with metastatic castration-resistant prostate cancer. *Clin Cancer Res* 2016;22:3774–81.
19. de Bruijn P, de Graan AJ, Nieuweboer A, Mathijssen RH, Lam MH, de Wit R, et al. Quantification of cabazitaxel in human plasma by liquid chromatography/triple-quadrupole mass spectrometry: a practical solution for non-specific binding. *J Pharm Biomed Anal* 2012;59:117–22.
20. Del Re M, Fogli S, Derosa L, Massari F, De Souza P, Crucitta S, et al. The role of drug-drug interactions in prostate cancer treatment: focus on abiraterone acetate/prednisone and enzalutamide. *Cancer Treat Rev* 2017;55:71–82.
21. Eisenberger M, Hardy-Bessard AC, Kim CS, Geczi L, Ford D, Mourey L, et al. Phase III study comparing a reduced dose of cabazitaxel (20 mg/m²) and the currently approved dose (25 mg/m²) in postdocetaxel patients with metastatic castration-resistant prostate cancer-PROSELICA. *J Clin Oncol* 2017;35:3198–206.
22. de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, 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.
23. van Soest RJ, Nieuweboer AJ, de Morree ES, Chitu D, Bergman AM, Goey SH, et al. The influence of prior novel androgen receptor targeted therapy on the efficacy of cabazitaxel in men with metastatic castration-resistant prostate cancer. *Eur J Cancer* 2015;51:2562–9.

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