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RESEARCH LETTER

Influence of Darolutamide on Cabazitaxel Systemic Exposure

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Patients with metastatic prostate cancer currently receive taxane chemotherapy or androgen receptor signalling inhibitors (ARSIs) already in the hormone-sensitive stage. Because of this extensive treatment history, patients with metastatic castration-resistant prostate cancer (mCRPC) are further prone to drug resistance as a result of cross-resistance and clonal evolution of therapy-resistant clones [1]. The taxane cabazitaxel, reserved for patients with mCRPC after progression on docetaxel, is often perceived as an option of last resort in this population. Therefore, strategies to overcome drug resistance to cabazitaxel are highly desired.

It has been reported that resistance to cabazitaxel in prostate cancer models can be alleviated by concomitant treatment with the ARSI enzalutamide, even in tumours that also harbour enzalutamide resistance [2]. Unfortunately, clinical testing of this combination revealed that the potentially synergistic action was hampered by a negative pharmacokinetic effect. Enzalutamide is a strong cytochrome P450 3A4 inducer that caused a clinically relevant reduction in cabazitaxel systemic exposure of 22% after 6 weeks [3]. A combination of a taxane and an ARSI without a pharmacokinetic interaction is therefore essential. Darolutamide is an ARSI with low drug–drug interaction potential that is currently approved for the treatment of non-metastatic castration-resistant prostate cancer [4]. Clinical data showed only a 29% decrease of midazolam concentrations, a sensitive cytochrome P450 3A4 substrate, by darolutamide, compared with a 86% decrease by enzalutamide [5]. The magnitude of this effect on cabazitaxel concentrations is currently unknown. Here, we report the outcomes of the influence of darolutamide on cabazitaxel plasma exposure in patients with mCRPC.

Patients with mCRPC with prior docetaxel treatment, without ARSI treatment in the prior 6 weeks, were eligible. Patients receiving cabazitaxel monotherapy (up to 20 mg/m^2 every 3 weeks) were enrolled on day 1 and received concomitant darolutamide (600 mg twice daily with food) from day 2 onwards for a maximal 12 weeks. During cabazitaxel infusion on day 1 and after 6 and 12 weeks of darolutamide co-treatment, patients underwent 24-h pharmacokinetic sampling. Samples were obtained before drug administration and 0.5, 0.92, 1.08, 1.25, 1.5, 2, 3, 5, 7, 12 and 24 h after drug administration. Cabazitaxel and darolutamide plasma concentrations were measured using validated liquid chromatography/tandem mass spectrometry methods [6]. The lower limit of quantification was 1.00 ng/mL for both drugs. The primary endpoint was the difference between the area under the curve from 0 to 24 h ($AUC_{0–24h}$) of cabazitaxel without and after 6 weeks of concomitant darolutamide. Individual pharmacokinetic parameters were estimated using a linear/log trapezoidal non-compartmental analysis using Phoenix WinNonLin 8.3 (Pharsight, Mountain View, CA, USA). The maximum concentration was based on observed concentrations. Eighteen evaluable patients were required to detect a clinically relevant difference in $AUC_{0–24h}$ of at least 20%, based on a within-patient standard deviation of 30%, 80% power and a two-sided α of 5%, using a paired t-test on log transformed data. Secondary endpoints were other pharmacokinetic parameters of cabazitaxel, pharmacokinetics of darolutamide and darolutamide treatment-emergent adverse events, which were scored according to Common Terminology Criteria for Adverse Events version 5.0. This trial was registered at the Netherlands Trial Register under NL8611.

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Between September 2020 and November 2021, 20 patients with mCRPC with an indication for cabazitaxel were enrolled. Fifteen patients had already started treatment with cabazitaxel, having received a median of two cycles. Two patients did not reach the primary endpoint because of disease progression. Baseline characteristics are provided in Table S1 of the Electronic Supplementary Material (ESM). In 18 patients, cabazitaxel plasma concentrations after 6 weeks of darolutamide were not significantly different from cabazitaxel monotherapy (AUC_{0-24h}: −4%; 95% confidence interval − 19 to + 13; $p = 0.58$; Fig. 1A). In addition, after 12 weeks of darolutamide, cabazitaxel systemic exposure was not significantly different in 12 patients (AUC_{0-24h}: + 4%; 95% confidence interval − 10 to + 20; $p = 0.54$; Fig. 1B). Darolutamide plasma concentrations (geometric mean AUC_{0-12h} [coefficient of variation %]) in 18 patients after 6 weeks of treatment with darolutamide were 39,175 ng*h/mL (41%) and in 12 patients were 40,517 ng*h/mL (28%) after 12 weeks of treatment, respectively (Fig. 2). These were comparable to phase I studies on darolutamide, indicating that cabazitaxel has no influence on darolutamide

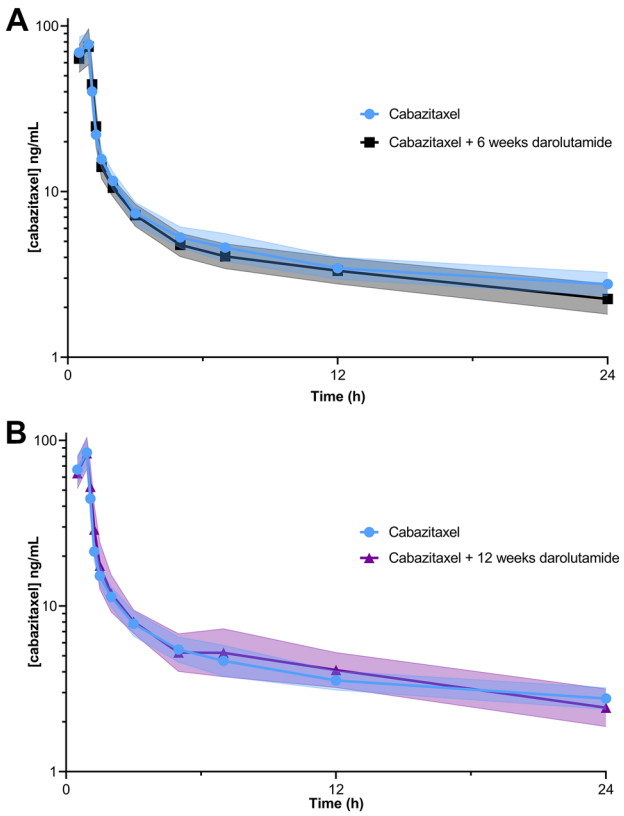

Fig. 1 Plasma concentrations of cabazitaxel with and without darolutamide treatment for 6 weeks in 18 patients (**A**) and for 12 weeks in 12 patients (**B**). Dose-corrected (to 20 mg/m^2) geometric mean plasma concentration versus time profiles from 0 to 24 hours (h) after the start of the infusion are shown. Confidence bands indicate the 95% confidence interval

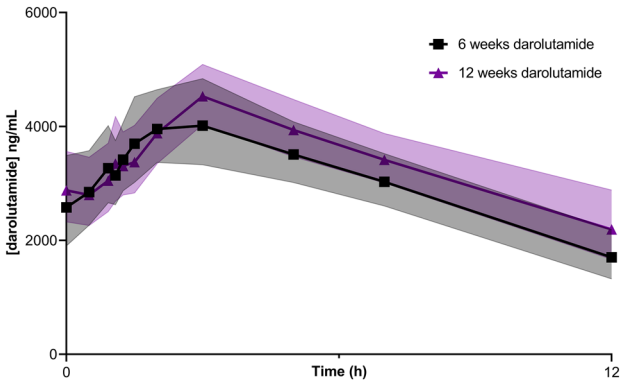

Fig. 2 Plasma concentrations of darolutamide depicted as area under the curve from 0 to 24 hours (h) after darolutamide treatment for 6 weeks ($n = 18$) and 12 weeks ($n = 12$). Geometric mean plasma concentration versus time profiles from 0 to 12 h after oral intake of darolutamide (simultaneously with the start of cabazitaxel infusion) are shown. No dose correction was performed, as all patients received similar doses of darolutamide throughout the study period. Confidence bands indicate the 95% confidence interval

exposure [5]. Additional pharmacokinetic parameters of cabazitaxel and darolutamide are listed in Table S2 and S3 of the ESM, respectively. Darolutamide treatment-emergent adverse events after 6 weeks of combination treatment (defined as the sum of adverse events after 6 weeks of combination treatment minus the sum of adverse events during treatment with cabazitaxel alone) included anaemia, anorexia, constipation, diarrhoea, nausea, oedema, pain in extremities and vomiting and were grade 1 or 2 (Table S4 of the ESM).

Ever since dosing cabazitaxel at 20 mg/m^2 was proven to be non-inferior to 25 mg/m^2, 20 mg/m^2 has become the standard of care [7]. The consequences of further reductions in plasma exposure are unknown. Therefore, caution is required when combining drugs with cabazitaxel. Here, we show that from a pharmacokinetic perspective, cabazitaxel and darolutamide can be safely combined in patients with mCRPC, even with the 20 mg/m^2 dose.

Our findings pave the way for testing the efficacy of this promising combination in an era of combination regimes for prostate cancer. The ENZAMET trial did not show a benefit of enzalutamide in patients receiving docetaxel in the setting of metastatic castration-naïve prostate cancer, which may have been caused by reduced docetaxel exposure, as docetaxel metabolism highly resembles that of cabazitaxel [8]. In contrast, PEACE-1 showed a robust benefit of the addition of abiraterone to docetaxel in metastatic castration-naïve prostate cancer, fuelling the rationale for studies investigating the combination of taxanes with ARSIs [9]. The ARASENS phase III trial, investigating the addition of darolutamide to docetaxel, has already proven the enhanced effectiveness of this combination, which as reported here

should be devoid of a detrimental cytochrome P450 3A4 drug interaction. Patients with metastatic castration-naïve prostate cancer treated with the combination regimen were found to have a significantly improved overall survival compared with patients treated with docetaxel [10]. Further studies of the combined use of darolutamide and cabazitaxel are equally warranted.

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Declarations

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Conflicts of Interest/Competing Interests HW: honoraria; Astellas and Roche and travel expenses; Astellas and Ipsen. PH: consulting fees; Astellas, MSD, Pfizer, AstraZeneca, BMS and Ipsen. MPL: advisory role/speaker fees; Incyte, Amgen, Janssen Cilag B.V., Bayer, Servier, Roche, Pfizer Sanofi Aventis Netherlands BV and Astellas and has received research funding (institutional) from Sanofi, JnJ, Merck and Astellas. RDW: advisory role/speaker fees; Sanofi, Merck, Lilly, Roche, Bayer, Janssen Cilag B.V. and Clovis and research funding (institutional); Sanofi and Bayer. RHJM: has received research funding (institutional) from Bayer, Sanofi and Astellas.

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