Brief Correspondence

Plasma Androgen Receptor and Docetaxel for Metastatic Castration-resistant Prostate Cancer

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Article info

Abstract

Plasma androgen receptor (*AR*) gain identifies metastatic castration-resistant prostate cancer (mCRPC) patients with worse outcome on abiraterone/enzalutamide, but its relevance in the context of taxane chemotherapy is unknown. We aimed to evaluate whether docetaxel is active regardless of plasma *AR* and to perform an exploratory analysis to compare docetaxel with abiraterone/enzalutamide. This multi-institutional study was a pooled analysis of *AR* status, determined by droplet digital polymerase chain reaction, on pretreatment plasma samples. We evaluated associations between plasma *AR* and overall/progression-free survival (OS/PFS) and prostate-specific antigen (PSA) response rate in 163 docetaxel-treated patients. OS was significantly shorter in case of *AR* gain (hazard ratio [HR] = 1.61, 95% confidence interval [CI] = 1.08–2.39, $p = 0.018$), but not PFS (HR = 1.04, 95% CI 0.74–1.46, $p = 0.8$) or PSA response (odds ratio = 1.14, 95% CI = 0.65–1.99, $p = 0.7$). We investigated the interaction between plasma *AR* and treatment type after incorporating updated data from our prior study of 73 chemotherapy-

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naïve, abiraterone/enzalutamide-treated patients, with data from 115 first-line docetaxel patients. In an exploratory analysis of mCRPC patients receiving first-line therapies, a significant interaction was observed between plasma *AR* and docetaxel versus abiraterone/enzalutamide for OS (HR = 0.16, 95% CI = 0.06–0.46, $p < 0.001$) and PFS (HR = 0.31, 95% CI = 0.12–0.80, $p = 0.02$). Specifically, we reported a significant difference for OS favoring abiraterone/enzalutamide for *AR*-normal patients (HR = 1.93, 95% CI = 1.19–3.12, $p = 0.008$) and a suggestion favoring docetaxel for *AR*-gained patients (HR = 0.53, 95% CI = 0.24–1.16, $p = 0.11$). These data suggest that *AR*-normal patients should receive abiraterone/enzalutamide and *AR*-gained could benefit from docetaxel. This treatment selection merits prospective evaluation in a randomized trial.
Patient summary: We investigated whether plasma androgen receptor (*AR*) predicted outcome in metastatic castration-resistant prostate cancer (mCRPC) patients treated with docetaxel, and we performed an exploratory analysis in patients treated with docetaxel or AR-directed drugs as first-line mCRPC therapy. We showed that plasma *AR* normal favored hormonal treatment, whilst plasma *AR*-gained patients may have had a longer response to docetaxel, suggesting that plasma *AR* status could be a useful treatment selection biomarker.

There are currently several approved life-prolonging therapies for the treatment of metastatic castration-resistant prostate cancer (mCRPC), including androgen receptor (AR)-directed drugs and taxanes. Plasma DNA analysis from mCRPC patients has suggested potential clinical applicability with an association between plasma *AR* aberrations and worse outcome with AR-directed drugs [1–5]. To date, detection of AR splice variants has been shown to have potential utility for the selection of taxane versus AR-targeted therapy for patients with mCRPC [6,7]. However, the relevance of plasma *AR* status in the context of taxanes is unknown.

We here aimed to evaluate the association of plasma *AR* status with outcomes in mCRPC patients treated with docetaxel. Additionally, we aimed to perform an exploratory analysis to compare the difference in outcome by plasma *AR* status for patients treated either with first-line docetaxel or AR-directed therapy.

Plasma samples were collected, with the primary aim of biomarker evaluation, from mCRPC patients, treated with standard-dose intravenous docetaxel 75 mg/m^2 every 3 wk with prednisone 5 mg twice daily for a maximum of 10 cycles for mCRPC [8], between May 2011 and January 2017 in 20 institutions. For the exploratory analysis, we included data on patients from our previous publication [5] who received abiraterone/enzalutamide prior to chemotherapy at the development of mCRPC, with updated clinical follow-up with a cut-off date of December 2017. All patients provided signed consent to an institutional review board-approved protocol before sample collection. Selection criteria, procedures, and the *AR* copy number (CN) droplet digital polymerase chain reaction assay are described in the Supplementary material.

We set out to determine *AR* status in plasma collected from 166 docetaxel-treated mCRPC patients prior to first- or second-line mCRPC therapy (Fig. 1A), but we had sample failure in three cases. We detected plasma *AR* gain in 50 patients (31%; 28% *AR* gain prior to first-line and 37% prior to second-line therapy). The median number of docetaxel cycles was the same in *AR*-normal and *AR*-gained

patients (median 8, interquartile range 6–10). The median follow-up period of alive patients was 24 mo. As 98% of the deaths were prostate cancer related, only overall survival (OS), and not cancer-specific survival, was analyzed. The median OS was 14 mo (95% confidence interval [CI] 12–23) for *AR*-gained patients and 22 mo (95% CI 20–29) for *AR*-normal patients. Median progression-free survival (PFS) was 7 mo (95% CI 5–8) in *AR*-gained patients and 7 mo (95% CI 6–8) in *AR*-normal patients. OS was significantly shorter in *AR*-gained versus *AR*-normal patients (hazard ratio [HR] = 1.61, 95% CI 1.08–2.39, $p = 0.02$), but no significant difference was observed for PFS (HR = 1.04, 95% CI 0.74–1.46, $p = 0.8$) or prostate-specific antigen (PSA) decline ≥50% (odds ratio = 1.14, 95% CI 0.65–1.99, $p = 0.7$; Fig. 1B–D).

Next, we selected the 115 patients treated with docetaxel as first-line therapy and in an exploratory, analysis compared them with 73 previously described patients treated with first-line abiraterone/enzalutamide (Fig. 1A) [5]. A comparison of clinicopathological characteristics between patients receiving either docetaxel or abiraterone/enzalutamide as first-line therapy showed significant differences in age, site of metastases, PSA, lactate dehydrogenase (LDH), hemoglobin, alkaline phosphatase, and plasma *AR* status (Supplementary Table 1). When comparing *AR*-normal with *AR*-gained patients in each treatment group, serum LDH and PSA were significantly higher in *AR*-gained patients treated with abiraterone/enzalutamide and serum alkaline phosphatase was significantly higher in plasma *AR*-gained patients treated with docetaxel (Supplementary Table 2).

The interaction of docetaxel or abiraterone/enzalutamide therapy and *AR* status was investigated using a multivariable Cox proportional hazard model, which showed a significant treatment interaction with *AR* status for both OS (HR = 0.16, 95% CI 0.06–0.46, $p < 0.001$) and PFS (HR = 0.31, 95% CI 0.12–0.80, $p = 0.02$; Supplementary Table 3). The median follow-up period for alive patients of the abiraterone/enzalutamide cohort was 32 mo.

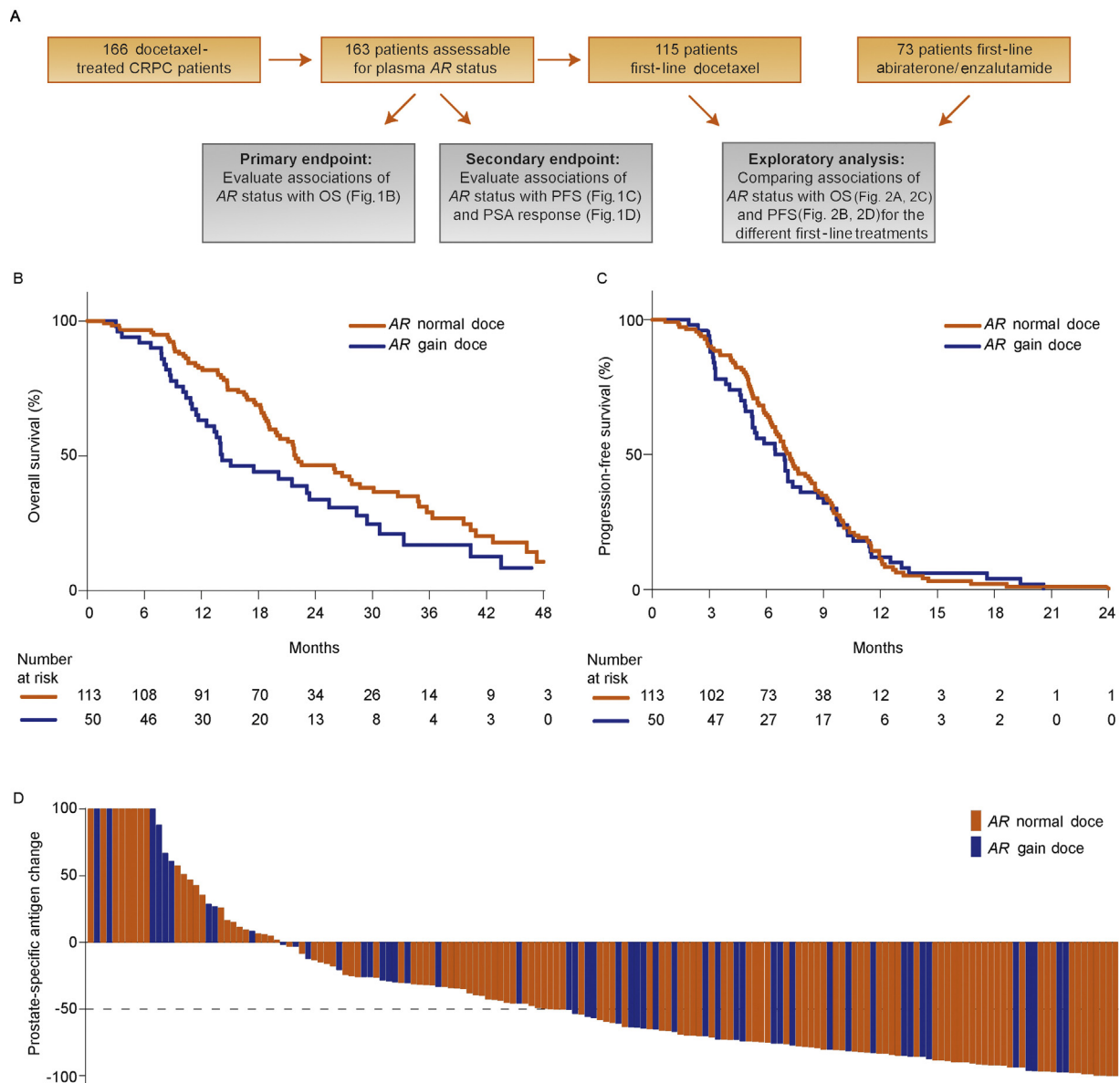The estimated median OS and PFS as a function of treatment and *AR* CN status are depicted in Figures 2A and
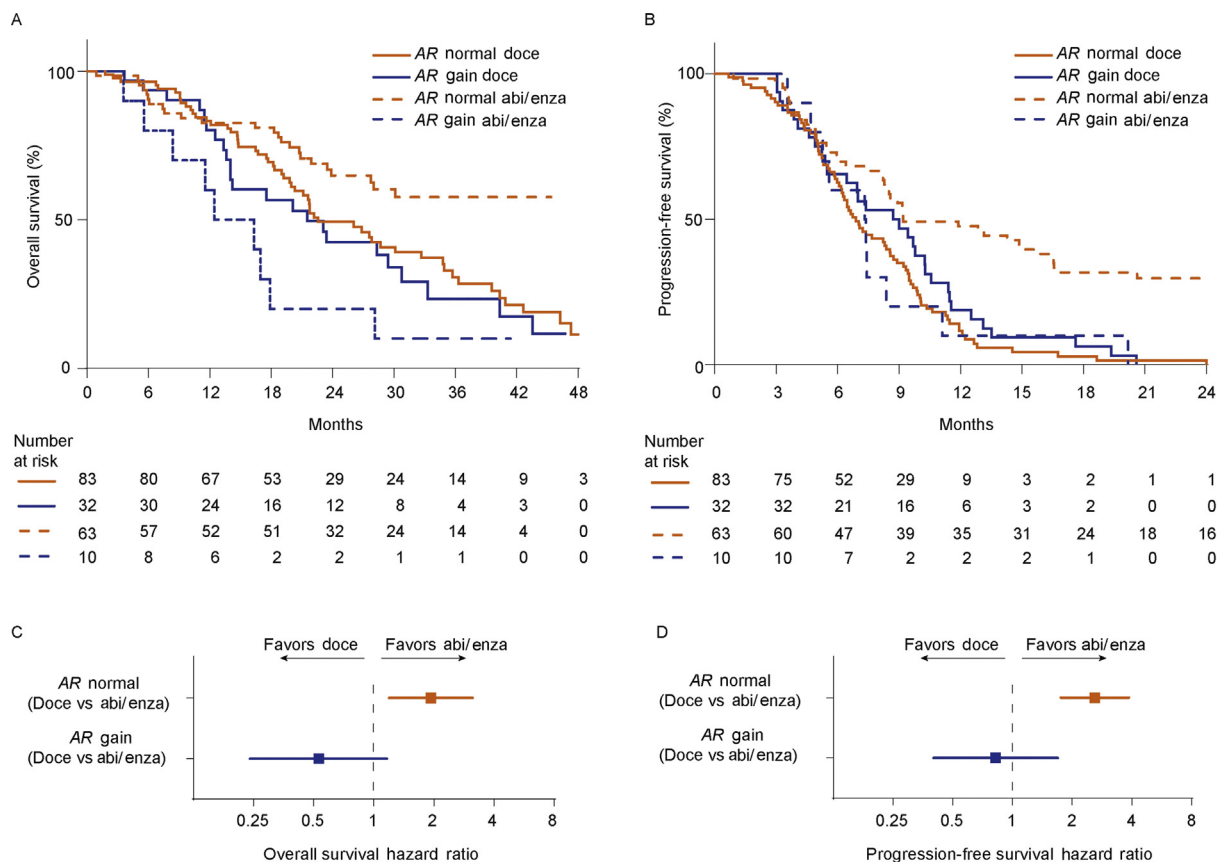
Fig. 1 – Study design and association of plasma *AR* status with clinical outcome in castration-resistant prostate cancer patients treated with docetaxel. (A) Flow chart showing the selection of docetaxel-treated patients for the primary and exploratory analyses. (B) Overall survival and (C) progression-free survival in docetaxel-treated patients. (D) Waterfall plots depicting prostate-specific antigen (PSA) declines (%) by *AR* copy number normal and gain in docetaxel-treated patients. Bars clipped at maximum 100%. AR = androgen receptor; CN = copy number; CRPC = castration-resistant prostate cancer; doce = docetaxel; OS = overall survival; PFS = progression-free survival.

2B, respectively. The HRs for OS (Fig. 2C) and PFS (Fig. 2D) estimated from the Cox proportional hazard regression analyses suggested that *AR*-normal patients treated with abiraterone/enzalutamide had a significantly lower risk of death (HR = 1.93, 95% CI 1.19–3.12, p = 0.008) and progressive disease (HR = 2.60, 95% CI 1.75–3.86, p < 0.001) when compared with those treated with docetaxel, and in *AR*-gained patients there was a suggestion toward a lower risk of death (HR = 0.53, 95% CI 0.24–1.16, p = 0.11; Fig. 2C) and progressive disease (HR = 0.82, 95% CI 0.40–1.69, p = 0.6; Fig. 2D) with docetaxel compared with abiraterone/enzalutamide therapy. In multivariable analysis of first-line treatment patients, including treatment type, plasma *AR* status, and other pretreatment baseline features previously

shown to be clinically relevant [5], we observed that plasma *AR* gain was independently associated with worse OS (HR = 6.55, 95% CI 2.74–15.68, p < 0.001) and PFS (HR = 3.24, 95% CI 1.47–7.14, p = 0.004; Supplementary Table 3).

Metastatic CRPC patients can be treated with docetaxel or AR-targeting therapies as first-line therapy. We and others have reported that detection of circulating *AR* aberrations is associated with worse outcome on abiraterone/enzalutamide [2–5]. In this study, we report that plasma *AR* gain in docetaxel-treated patients was associated with significantly shorter OS. This emphasizes the urgent clinical need of alternative treatments for *AR*-gained patients [9]. Retrospective studies have suggested that

Fig. 2 – Association of plasma *AR* status with clinical outcome in castration-resistant prostate cancer patients treated with either docetaxel or AR-directed therapies (abiraterone or enzalutamide) as first-line treatment. Interaction between *AR* status and treatment type, after including data from abiraterone- or enzalutamide-treated patients for (A) OS and (B) PFS. (C) Forest plot shows the hazard ratio and 95% confidence interval for (C) OS and (D) PFS in *AR*-normal and *AR*-gained patients. Abi = abiraterone, *AR* = androgen receptor; doce = docetaxel; enza = enzalutamide; OS = overall survival; PFS = progression-free survival.

AR-V7 expression in mCRPC men can be considered a treatment-specific biomarker associated with superior survival for taxane therapy compared with AR therapies [6,7]. Here, we explored whether plasma *AR* gain status is associated with resistance to taxanes in an abiraterone/enzalutamide-naïve population and, to avoid the influence of possible cross-resistance events on the interpretation of survival data, we compared it with the effect seen in taxane-naïve abiraterone/enzalutamide-treated patients [10]. The absence of a difference in outcome by *AR* status in treatment-naïve docetaxel-treated patients introduces the hypothesis that *AR*-gained patients would derive greater benefit from treatment with taxanes in preference to abiraterone/enzalutamide. However, we recognize some limitations of our study, including the significantly different durations of median follow-up of alive patients between the docetaxel and the abiraterone/enzalutamide cohort (24 vs 32 mo, with overall follow-up of 24 mo); the relatively modest sample size of the cohorts, especially of *AR*-gained patients treated with abiraterone/enzalutamide (*n* = 10); and the retrospective, nonrandomized design. The majority of patients were treated with taxanes in centers when abiraterone or enzalutamide were not widely available prior to chemotherapy. Nonetheless, there could be a bias due to

patient selection, given the different toxicity profiles of taxanes compared with AR-targeting drugs. Additionally, detection of an *AR*-gained clone may be more likely at higher circulating tumor fraction that in itself is prognostic; this could bias the ability to ascertain the predictive value of plasma *AR* with AR-targeting drugs but would not change the interpretation of the absence of difference in our treatment-naive taxane-treated cohort. Lastly, we only considered *AR* gain, but other concurrently assessed AR aberrations (somatic point mutations or splice variants) could provide additional or overlapping information. Our findings suggest that *AR* gain detected in plasma is associated with resistance to abiraterone/enzalutamide but not with taxanes when used in the first-line setting. In conclusion, prospective randomized trials are warranted to validate the utility of plasma *AR* status for treatment selection in mCRPC patients.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.09.049.

References

[1] Annala M, Vandekerkhove G, Khalaf D, et al. Circulating tumor DNA genomics correlate with resistance to abiraterone and enzalutamide in prostate cancer. Cancer Discov 2018;8:444–57.

[2] Romanel A, Tandefelt DG, Conteduca V, et al. Plasma AR and abiraterone-resistant prostate cancer. Sci Transl Med 2015;312, 312re10.

[3] Salvi S, Casadio V, Conteduca V, et al. Circulating cell-free AR and CYP17A1 copy number variations may associate with outcome of metastatic castration-resistant prostate cancer patients treated with abiraterone. Br J Cancer 2015;112:1717–24.

[4] Salvi S, Casadio V, Conteduca V, et al. Circulating AR copy number and outcome to enzalutamide in docetaxel-treated metastatic castration-resistant prostate cancer. Oncotarget 2016;7:37839–45.

[5] Conteduca V, Wetterskog D, Sharabiani MTA, et al. Androgen receptor gene status in plasma DNA associates with worse outcome on enzalutamide or abiraterone for castration-resistant prostate cancer: a multiinstitution correlative biomarker study. Ann Oncol 2017;28:1508–16.

[6] Antonarakis ES, Lu C, Luber B, et al. Androgen receptor splice variant 7 and efficacy of taxane chemotherapy in patients with metastatic castration-resistant prostate cancer. JAMA Oncol 2015;1:582–91.

[7] Scher HI, Graf RP, Schreiber NA, et al. Nuclear-specific AR-V7 protein localization is necessary to guide treatment selection in metastatic castration-resistant prostate cancer. Eur Urol 2017;71:874–82.

[8] Tannock IF, de Wit R, Berry WR, et al. TAX 327 Investigators. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351:1502–12.

[9] van Soest RJ. Liquid biopsies and plasma DNA: paving the way for personalized medicine in metastatic castration-resistant prostate cancer. Ann Oncol 2017;28:1408–9.

[10] van Soest RJ, de Morrée ES, Kweldam CF, et al. Targeting the androgen receptor confers in vivo cross-resistance between enzalutamide and docetaxel, but not cabazitaxel, in castration-resistant prostate cancer. Eur Urol 2015;67:981–5.