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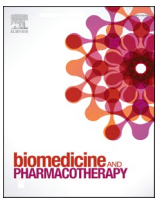

A common germline variant in *CYP11B1* is associated with adverse clinical outcome of treatment with abiraterone or enzalutamide

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ABSTRACT

Extragonadal androgens play a pivotal role in prostate cancer disease progression on androgen receptor signaling inhibitors (ARSi), including abiraterone and enzalutamide. We aimed to investigate if germline variants in genes involved in extragonadal androgen synthesis contribute to resistance to ARSi and may predict clinical outcomes on ARSi. We included ARSi naive metastatic prostate cancer patients treated with abiraterone or enzalutamide and determined 18 germline variants in six genes involved in extragonadal androgen synthesis. Variants were tested in univariate and multivariable analysis for the relation with overall survival (OS) and time to progression (TTP) by Cox regression, and PSA response by logistic regression. A total of 275 patients were included. From the investigated genes *CYP17A1*, *HSD3B1*, *CYP11B1*, *AKR1C3*, *SRD5A1* and *SRD5A2*, only rs4736349 in *CYP11B1* in homozygous form (TT), present in 54 patients (20%), was related with a significantly worse OS (HR = 1.71, 95% CI 1.09 – 2.68, p = 0.019) and TTP (HR = 1.50, 95% CI 1.08 – 2.09, p = 0.016), and was related with a significantly less frequent PSA response (OR = 0.48, 95% CI 0.24 – 0.96, p = 0.038) on abiraterone or enzalutamide in a multivariable analysis. The frequent germline variant rs4736349 in *CYP11B1* is, as homozygote, an independent negative prognostic factor for treatment with abiraterone or enzalutamide in ARSi naive metastatic prostate cancer patients. Our findings warrant prospective investigation of this potentially important predictive biomarker.

1. Introduction

Prostate cancer is the most prevalent type of cancer in men worldwide [1]. Ever since it is known that prostate cancer is androgen driven, androgen deprivation therapy (ADT) by surgical or chemical castration, is the mainstay in the treatment [2]. While downregulation of testicular androgen synthesis is efficacious at first, patients inevitably progress to castration-resistant prostate cancer (CRPC) [3]. It has become clear that extragonadal sources of androgens play a pivotal role in the emergence of castration resistance. Adrenal precursor steroids can be converted to androgen precursors or androgens by a cascade of enzymatic reactions (Fig. 1). Androgen precursors are transformed to potent androgens in the tumor cell, resulting in androgen receptor (AR) stimulation and transcription of AR regulated oncogenes [4,5]. With the advent of second generation AR signaling inhibitors (ARSi), such as abiraterone and enzalutamide, the tumor promoting effects of extragonadal androgens can be counteracted. Abiraterone inhibits CYP17A1, which plays a critical role in the synthesis of adrenal androgens [6]. After its approval in metastatic CRPC, both before and after docetaxel treatment, abiraterone with prednisone was also approved for metastatic castration naive prostate cancer (CNPC) [7–9]. Enzalutamide is a competitive AR antagonist which prevents ligand binding to the AR and subsequent

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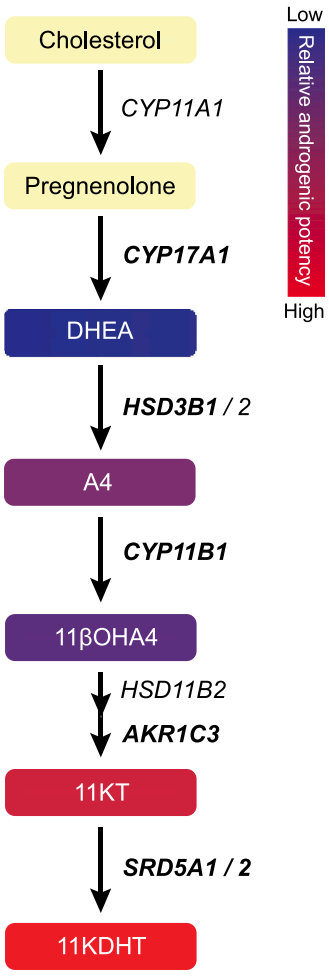

Fig. 1. Extragonadal androgen synthesis pathway. Genes investigated for germline variants are depicted in bold. Relative androgenic potency of the substrates is indicated. Abbreviations: DHEA: dehydroepiandrosterone, A4: androstenedione, 11βOHA4: 11-beta-hydroxy-androstenedione, 11KT: 11-keto-testosterone, 11KDHT: 11-ketodihydrotestosterone.

nuclear translocation. Equal to abiraterone, enzalutamide has been approved for treatment of metastatic CRPC, before and after docetaxel, as well as for metastatic CNPC [10–12].

Despite generally robust survival benefits with first line ARSi, outcomes are highly variable among patients due to acquired resistance [13]. We hypothesize that germline variants in genes involved in extragonadal androgen synthesis contribute to resistance to abiraterone and enzalutamide. In this study, we investigated the impact of germline variants in the extragonadal androgen synthesis pathway on clinical outcomes of ARSi naive metastatic prostate cancer patients treated with abiraterone or enzalutamide.

2. Patients and methods

2.1. Study design

For this retrospective analysis, we included ARSi naive metastatic prostate cancer patients independent of progression status on ADT who were treated with abiraterone or enzalutamide between 2010 and March 2023 in the Erasmus Medical Center Cancer Institute (Rotterdam) or the Netherlands Cancer Institute (Amsterdam). From patients at the Erasmus MC, written informed consent was obtained for collection of a blood sample for genotyping (local protocol: MEC-02–1002), while samples from patients at the Netherlands Cancer Institute were collected as part of routine care. Sample and data transfer was approved by the Institutional Review Board of the Netherlands Cancer Institute (IRBdm21–161). Patients treated at the Erasmus MC served as the discovery cohort, while the total study cohort was used as the replication cohort, since the data from only the Netherlands Cancer Institute were not mature enough to serve as replication cohort (i.e. not sufficient progression or OS events were reached, resulting in censoring from the survival analyses). We selected 18 germline variants in six genes involved in extragonadal androgen synthesis for which relations with survival outcomes of prostate cancer patients on ADT or ARSi were previously investigated (Supplementary Table 1). Germline variants in the following genes were investigated: *CYP17A1*, *HSD3B1*, *CYP11B1*, *AKR1C3*, *SRD5A1* and *SRD5A2* (Fig. 1).

2.2. DNA isolation and genotyping

DNA was isolated from whole blood and plasma samples collected in EDTA tubes, with a Maxwell (Promega, Madison, WI, USA) using the Maxwell RSC Whole Blood DNA kit (Promega) or a QIAsymphony (Qiagen, Hilden, Germany) using the DSP DNA Midi kit (Qiagen). Genotyping was performed using a TaqMan 7500 Real-Time PCR System (Applied Biosystems, Waltham, MA, USA) with TaqMan® SNP Genotyping Assays with allele-specific primers and probes (Applied Biosystems; Supplementary Table 2) following standard settings or a Bio-Rad QX200 Droplet generator and a Bio-Rad T100 Thermal Cycler with a QX200 Droplet Reader (Bio-Rad Laboratories, Hercules, CA, USA) for rs1047303 and rs1856888 in case of insufficient DNA quantity for Real-Time PCR. Digital droplet PCR consisted of 39 cycles. Each cycle consisted of denaturation (95 °C for 10:30 min), annealing (55 °C for 1:00 min), and elongation (98 °C for 10:00 min). Results were validated by Sanger Sequencing.

2.3. Study outcomes

Overall survival (OS) was defined as the time from initiation of ARSi therapy until death by any cause. Time to progression (TTP) was defined as the time from initiation of ARSi therapy until clinical, biochemical or radiological progression, at the discretion of the treating physician. Prostate-specific antigen (PSA) response was defined as a decline in PSA of $> 50\%$ during ARSi therapy compared to baseline.

2.4. Statistical analysis

The observed allele frequencies were tested for Hardy-Weinberg equilibrium (HWE) using a chi-squared test. Linkage disequilibrium (LD) was tested for germline variants on the same gene using PLINK (Supplementary Table 1) [14]. The cut-off for LD was set at $R^2 > 0.8$. Haplotypes were classified based on the presence of variants: wild type if none, heterozygous if ≥ 1 heterozygous variant, or homozygous if ≥ 1 homozygous variant. Germline variants or haplotypes were fitted in additive, dominant and recessive models. The genetic model returning the lowest p value was used for further analysis. Genetic models in the discovery cohort (patients treated at the Erasmus MC) and baseline factors in the discovery cohort and the total cohort were tested against efficacy endpoints by Cox regression for time to event endpoints and by logistic regression for PSA response. Relations with $p < 0.1$ were tested in multivariable analyses using Cox or logistic regression with backward selection in the discovery cohort and – if not eliminated by backward selection – subsequently in the total study cohort. The following baseline factors were tested: age, Eastern Cooperative Oncology Group (ECOG) performance status (1–2 vs. 0), previous chemotherapy (docetaxel, followed by cabazitaxel vs. only docetaxel vs. none), treatment (enzalutamide vs. abiraterone) and medical center of treatment (Erasmus MC vs. Netherlands Cancer Institute). Missing data points in baseline factors were imputed using multiple imputation, generating five datasets for pooling. Median OS and TTP were determined by the Kaplan Meier

method and median follow-up was determined by the reverse Kaplan Meier method. Statistical analyses were performed in SPSS version 28 (IBM, Armonk, NY, USA). A two-sided $p < 0.05$ was considered significant.

3. Results

3.1. Baseline and response characteristics

A total of 275 patients were included, of whom 116 patients in the discovery cohort (i.e. patients treated at the Erasmus MC). In total, 215 patients were treated with abiraterone and 60 were treated with enzalutamide. Median follow-up was 53.9 months and 35.1 months in the discovery cohort and in the total cohort, respectively. Baseline and response characteristics are depicted in Table 1.

3.2. Genotype and outcome

The variants *CYP11B1* rs4736349, *CYP17A1* rs2486758, the *HSD3B1* haplotype, *SRD5A2* rs12470143 and *SRD5A2* rs2208532 were related with OS in the discovery cohort in univariate analysis. For TTP and PSA response, there was a relation with *CYP11B1* rs4736349, the *HSD3B1* haplotype and *SRD5A1* rs1691053 (Supplementary Table 3).

The baseline factors ECOG Performance Status, treatment, age and previous chemotherapy were related with one or more outcome measures (Supplementary Table 4) and were added to the multivariable model(s). In multivariable analysis (Table 2), *CYP11B1* rs4736349 was significantly related with OS, TTP and PSA response. Median OS was 16.5 months (IQR 10.1 – 29.7) in the TT group versus 31.5 months (IQR 17.5 – 61.0) in the CC / CT group (HR = 2.28, 95% CI 1.27 – 4.08, p = 0.006; Fig. 2A). Median TTP was 2.7 months (IQR 2.3 – 9.0) in the TT group versus 9 months (IQR 4.0 – 17.9) in the CC / CT group (HR = 1.95, 95% CI 1.14 – 3.35, p = 0.016; Fig. 2B). There was a PSA response in 32% (6/19) of patients in the TT group versus in 70% (62/89) of patients in the CC / CT group (OR = 0.14, 95% CI 0.03 – 0.60, p = 0.008; Fig. 3A). Other significant relations were found between *CYP17A1* rs2486758 and OS (HR = 3.07, 95% CI 1.28 – 7.31, p = 0.012) and *SRD5A1* rs1691053 and TTP (HR = 0.53, 95% CI 0.32 – 0.86, p = 0.011; Table 2).

Table 1
Baseline and response characteristics.

	Discovery cohort (n = 116)	Total cohort (n = 275)
Age at baseline	67.6 (62.6–73.0)	71.1 (64.9–75.6)
Treatment		
Abiraterone	62 (53%)	215 (78%)
Enzalutamide	54 (47%)	60 (22%)
Previous chemotherapy		
None	39 (34%)	176 (64%)
Only docetaxel	45 (39%)	67 (24%)
Docetaxel, followed by cabazitaxel	32 (28%)	32 (12%)
ECOG Performance Status		
0	24 (21%)	109 (40%)
1–2	63 (54%)	132 (48%)
Unknown	29 (25%)	34 (12%)
PSA at baseline	58.0 (21.7–211.5)	29.2 (10.3–89.3)
Follow-up (months)	53.9 (48.1–74.0)	35.1 (25.4–52.1)
OS events	88 (76%)	124 (45%)
OS (months)	28.9 (16.1–43.9)	26.1 (19.2–37.7)
Progression events	108 (93%)	222 (81%)
TTP (months)	8.6 (3.2–17.7)	12.0 (5.3–23.3)
PSA response		
Yes	40 (34%)	189 (69%)
No	68 (59%)	78 (28%)
Unknown	8 (7%)	8 (3%)

Median with IQR or frequency is reported. Abbreviations: ECOG: Eastern Cooperative Oncology Group, OS: overall survival, TTP: time to progression

In multivariable analysis in the total cohort, *CYP11B1* rs4736349 remained significantly related with worse OS, TTP and PSA response (Table 3). Median OS was 29.9 months (IQR 16.0 – 69.5) in the TT group versus 44.8 months (IQR 22.0 – 83.5) in the CC / CT group (HR = 1.71, 95% CI 1.09 – 2.68, p = 0.019; Fig. 2C). Median TTP was 8.8 months (IQR 3.2 – 23.6) in the TT group versus 12.7 months (IQR 6.2 – 26.6) in the CC / CT group (HR = 1.50, 95% CI 1.08 – 2.09, p = 0.016; Fig. 2**D**). Patients in the TT group less frequently had a PSA response (59%; 32/54) compared to patients in the CC / CT group (74%; 158/213) (OR = 0.48, 95% CI 0.24 – 0.96, p = 0.038; Fig. 3B). The baseline factors ECOG Performance Status, age at baseline, previous chemotherapy and medical center were added to the multivariable model in case of a relation ($p < 0.1$) with the outcome measure (Supplementary Table 5).

4. Discussion

We investigated the impact of germline variants in genes involved in extragonadal androgen synthesis on clinical outcome of treatment with abiraterone or enzalutamide in ARSi naive metastatic prostate cancer patients. The rs4736349 germline variant in *CYP11B1* was significantly related with OS, TTP and PSA response in the discovery cohort and in the total cohort. Patients homozygous for the TT variant had a significantly shorter OS and TTP and less frequently had a PSA response, even after correction for baseline factors with prognostic value in a multivariable model. This qualifies the identified *CYP11B1* germline variant as an independent prognostic factor for ARSi naive metastatic prostate cancer patients treated with abiraterone or enzalutamide. Further investigation of this germline variant as a potential predictive biomarker for ARSi treatment in ARSi naive metastatic prostate cancer patients is therefore warranted. With a global prevalence of 20% – which is similar to the findings in our cohorts – the TT genotype is highly frequent, stressing the relevance of the identified germline variant [15].

To our knowledge, this is the first study that identifies this germline variant in *CYP11B1* to be associated with clinical outcomes in prostate cancer patients. Despite multiple attempts, no relation between this germline variant and response to ADT in prostate cancer patients has been identified [16,17]. Yet, the role of CYP11B1 (steroid 11β-hydroxylase) in AR driven progression of prostate cancer has been well described. CYP11B1 synthesizes 11-oxygenated androgens from androstenedione in the adrenal glands. Peripherally, these are converted to 11-ketotestosterone, which has an androgenic potency comparable to testosterone and is the most abundant androgen in patients on ADT and in CRPC patients [4,18–20]. Interestingly, abiraterone also lowers circulating levels of 11-oxygenated androgens and 11-ketotestosterone in CRPC patients. This effect was equally present in patients who did not receive concomitant prednisone, proving an evident role for abiraterone itself [21]. Enzalutamide equally inhibits the stimulatory effects of androgens, including 11-ketotestosterone by direct blockage of the ligand binding domain of the AR. Yet, 11-ketotestosterone eventually drives the AR, contributing to resistance to ARSi. Our data show a prominent role for CYP11B1 in the emergence of resistance to both drugs. Increased CYP11B1 activity could very well play a role in resistance to ARSi. While the functional consequence of the rs4736349 variant in *CYP11B1* is currently unknown, an explanation for the less favorable outcomes of patients with the TT genotype could be increased enzymatic activity and consequently increased production of 11-ketotestosterone precursors. Currently, several efforts are being undertaken for the development of inhibitors of the synthesis of 11-ketotestosterone. One specific CYP11B1 inhibitor, metyrapone, is available, but has not been tested in the context of prostate cancer [20]. Further studies should focus on independent validation of the current findings and should have sufficient statistical power to stratify for patients treated with direct AR antagonists and agents targeting androgen synthesis, such as abiraterone.

In contrast to previous reports, we did not identify a relation between

Table 2
Multivariable analysis of selected germline variants and haplotypes in the discovery cohort (n = 116).

Endpoint	Factor	Comparison	Hazard ratio (95% CI)	p value
Overall survival	*CYP11B1* rs4736349	TT vs. CT + CC	2.28 (1.27–4.08)	0.006
	HSD3B1 haplotype	HOM vs. HET. vs. WT		0.051
		HET vs. WT	0.95 (0.59–1.55)	0.847
		HOM vs. WT	2.12 (1.10–4.09)	0.026
	CYP17A1 rs2486758	CC vs. TC vs. TT		0.041
		TC vs. TT	1.19 (0.74–1.91)	0.470
		CC vs. TT	3.07 (1.28–7.31)	0.012
	Treatment	Enzalutamide vs. abiraterone	0.60 (0.37–0.96)	0.035
	Previous chemotherapy			< 0.001
	Only docetaxel		2.99 (1.65–5.40)	< 0.001
	Docetaxel, followed by cabazitaxel		5.21 (2.84–9.55)	< 0.001
Time to progression	*CYP11B1* rs4736349	TT vs. CT + CC	1.95 (1.14–3.35)	0.016
	SRD5A1 rs1691053	CC + TC vs. TT	0.53 (0.32–0.86)	0.011
	Previous chemotherapy			< 0.001
	Only docetaxel		1.75 (1.09–2.79)	0.020
	Docetaxel, followed by cabazitaxel		4.45 (2.65–7.49)	< 0.001
PSA response			**Odds ratio (95% CI)**	
	CYP11B1 rs4736349	TT vs. CT + CC	0.14 (0.03–0.60)	0.008
	SRD5A1 rs1691053	CC + TC vs. TT	3.69 (0.92–14.81)	0.066
	ECOG Performance Status	1–2 vs. 0	0.22 (0.06–0.92)	0.038
	Previous chemotherapy			
	Only docetaxel		0.22 (0.06–0.86)	0.029
	Docetaxel, followed by cabazitaxel		0.05 (0.01–0.20)	< 0.001

Abbreviations: ECOG: Eastern Cooperative Oncology Group, HOM: homozygous variant, HET: heterozygous variant, WT: wild type

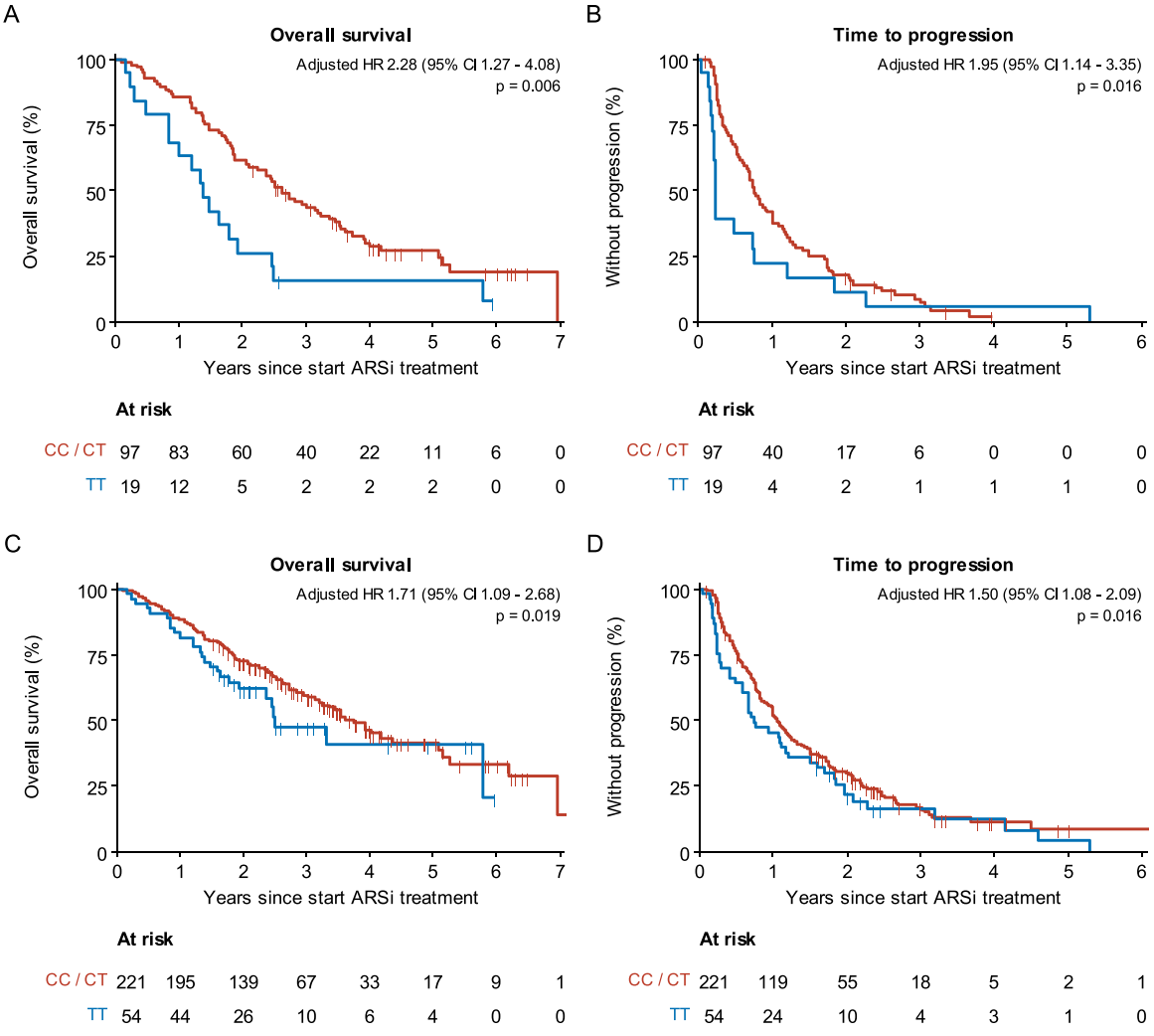

Fig. 2. Kaplan-Meier estimates for *CYP11B1* rs4736349 (homozygous variant (TT) versus wild type (CC) and heterozygous variant (CT)) in the discovery cohort (**A-B**) and the total cohort (**C-D**). Adjusted hazard ratios (HR) from multivariable Cox regression analyses with corresponding 95% CI and p value are depicted.

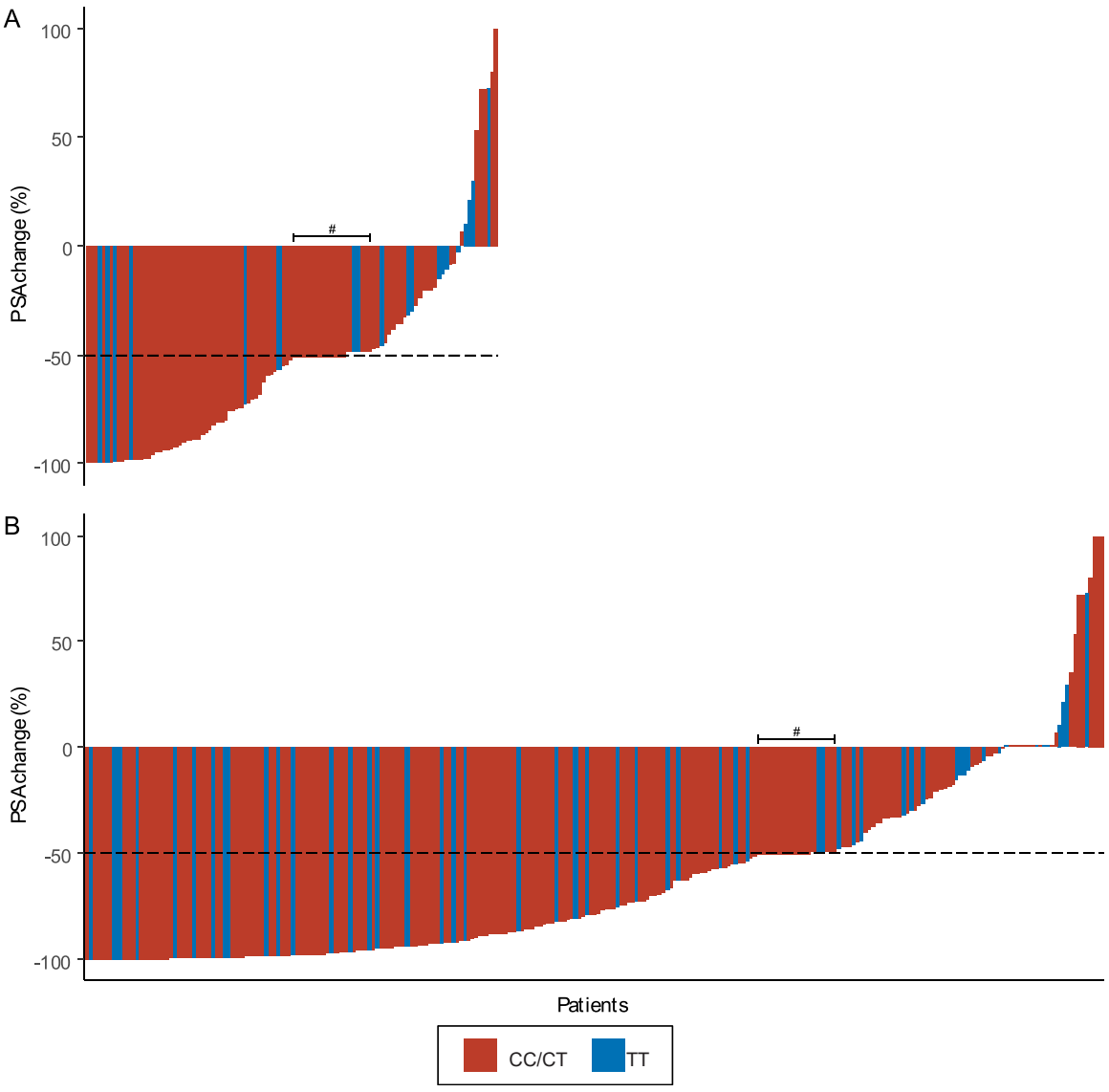

Fig. 3. Waterfall plots displaying best prostate-specific antigen (PSA) response to abiraterone or enzalutamide in the discovery cohort (**A,** n = 108) and in the total cohort (**B**, n = 267) in patients with the CC / CT versus the TT *CYP11B1* genotype. ($^{\#}$ PSA response status known, but PSA response value missing. Status depicted as −51% (responder) or − 49% (non-responder).).

rs1047303 in *HSD3B1* and response to abiraterone or enzalutamide. A retrospective analysis in 266 patients reported a shorter OS in patients homozygous for the variant, which remained significant after adjustment for baseline factors [22]. Another retrospective study in 547 patients reported adverse clinical outcomes with abiraterone or enzalutamide for patients homozygous for this variant, but none remained significantly related in multivariable analysis [23]. Furthermore, rs2486758 in *CYP17A1* was found to be related to worse response to abiraterone in two small retrospective studies in 60 and 87 mCRPC patients [24,25]. In the current report, only a relation between this variant and shorter OS was identified in the discovery cohort, remaining significant in multivariable analysis.

Strengths of this study are the use of multiple clinically relevant endpoints and the utilization of a multivariable model, taking established prognostic factors into account. Such corrections are essential, because of a high variability in prognosis among patients. Likewise, we corrected for variability between different study cohorts, which in this study is likely related to differences in extensiveness of disease history of patients at different medical centers. Medical center of treatment was therefore added as a variable to the multivariable model. This study is limited by its retrospective and explorative nature, refraining from correction for multiple testing, which increases the likelihood of false-positive results. Yet, because of the consistency of the findings among the discovery cohort and the total cohort, as well as among all three efficacy endpoints, further prospective studies on the impact of the *CYP11B1* germline variant are warranted. Findings in the discovery cohort could be replicated in the total cohort, consisting of patients treated at the Erasmus MC and the Netherlands Cancer Institute. Due to lack of maturity of data of patients treated at the Netherlands Cancer Institute, both cohorts were combined for validation of findings in the discovery cohort. Another limitation is the absence of additional baseline characteristics, such as Gleason score and metastatic burden in the multivariable analysis. These factors are known to impact prognosis and could therefore potentially lead to bias in the data.

In summary, in this study we have identified a common germline variant in *CYP11B1* that is related to response to abiraterone or enzalutamide in ARSi naive metastatic prostate cancer patients.

Table 3
Multivariable analysis of selected germline variants and haplotypes in the total cohort (n = 275).

Endpoint	Factor	Comparison	Hazard ratio (95% CI)	p value
Overall survival	*CYP11B1* rs4736349	TT vs. CT + CC	1.71 (1.09–2.68)	0.019
	Previous chemotherapy			
	Only docetaxel		1.92 (1.19–3.11)	0.008
	Docetaxel, followed by cabazitaxel		4.77 (2.76–8.22)	< 0.001
	ECOG Performance Status	1–2 vs. 0	2.12 (1.37–3.27)	< 0.001
	Medical Center	EMC vs. NCI	1.60 (0.98–2.61)	0.062
Time to progression	*CYP11B1* rs4736349	TT vs. CT + CC	1.50 (1.08–2.09)	0.016
	SRD5A1 rs1691053	CC + TC vs. TT	0.72 (0.51–1.01)	0.053
	Previous chemotherapy			
	Only docetaxel		1.53 (1.09–2.13)	0.014
	Docetaxel, followed by cabazitaxel		5.17 (3.40–7.86)	< 0.001
	ECOG Performance Status	1–2 vs. 0	1.54 (1.15–2.06)	0.004
	Age at baseline		0.98 (0.96–1.00)	0.014
PSA response			**Odds ratio (95% CI)**	
	CYP11B1 rs4736349	TT vs. CT + CC	0.48 (0.24–0.96)	0.038
	Previous chemotherapy			
	Only docetaxel		0.27 (0.13–0.54)	< 0.001
	Docetaxel, followed by cabazitaxel		0.09 (0.03–0.21)	< 0.001
	ECOG Performance Status	1–2 vs. 0	0.47 (0.25–0.90)	0.022
	Treatment	Enzalutamide vs. abiraterone	2.54 (1.12–5.72)	0.025

Abbreviations:: ECOG: Eastern Cooperative Oncology Group, EMC: Erasmus Medical Center, NCI: Netherlands Cancer Institute

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None.

CRediT authorship contribution statement

conception and design: SAJB, SLWK, RHJM. acquisition of data: SAJB, MM, FMFvO, EdJ, AMB, ADRH. analysis and interpretation of data: SAJB, FMFvO, EOdH, MJHC, TdW, RHNvS, RHJM. drafting of the manuscript: SAJB. critical revision of the manuscript for important intellectual content: all authors. statistical analysis: SAJB, FMFvO, EOdH. obtaining funding: RHNvS. supervision: SLWK, RdW, RHJM.

Declaration of Competing Interest

None.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopha.2023.115890.

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