CYP17A1 polymorphism c.-362T>C predicts clinical outcome in metastatic castration-resistance prostate cancer patients treated with abiraterone

Stefania Crucitta, Marzia Del Re, Federico Paolieri, Francesco Bloise, Andrea Sbrana, Enrico Sammarco, Chiara Mercinelli, et al.

Cancer Chemotherapy and Pharmacology

ISSN 0344-5704
Volume 86
Number 4

Cancer Chemother Pharmacol (2020)
86:527-533
DOI 10.1007/s00280-020-04133-w

Springer

Cancer Chemotherapy and Pharmacology (2020) 86:527–533
https://doi.org/10.1007/s00280-020-04133-w

ORIGINAL ARTICLE

CYP17A1 polymorphism c.-362T>C predicts clinical outcome in metastatic castration-resistance prostate cancer patients treated with abiraterone

Stefania Crucitta[1] · Marzia Del Re[1] · Federico Paolieri[2] · Francesco Bloise[2] · Andrea Sbrana[2] · Enrico Sammarco[2] · Chiara Mercinelli[2] · Federico Cucchiara[1] · Lorenzo Fontanelli[1] · Luca Galli[2] · Romano Danesi[1]

Received: 2 May 2020 / Accepted: 22 August 2020 / Published online: 18 September 2020

Abstract

Background Abiraterone became a standard hormonal therapy for patients with metastatic castration-resistance prostate cancer (mCRPC). However, patients may experience primary resistance to treatment. To date, few predictive biomarkers of efficacy have been identified. Our aim was to investigate the association between the single nucleotide polymorphism (SNP) c.-362T>C in the CYP17A1 gene, and clinical outcome in mCRPC patients treated with abiraterone.

Patients and methods mCRPC patients candidate to receive abiraterone were enrolled in the present retrospective pharmacogenetic study. Based on a literature selection, CYP17A1 rs2486758 (c.-362T > C) was selected and analysed by real-time PCR on genomic DNA extracted from whole blood. Univariate analysis was performed to test the association between the SNP and treatment-related clinical outcomes.

Results Sixty mCRPC patients were enrolled in the present study. Patients carrying the mutant CYP17A1 c.-362CT/CC genotypes showed a shorter median progression-free survival (PFS) and prostate-specific antigen-PFS (PSA-PFS) compared to patients carrying the TT genotype (10.7 vs 14.2 months and 8 vs 16 months, respectively; $p = 0.04$). No association between the selected SNP and the overall survival was found.

Conclusions These findings suggest an association between CYP17A1 c.-362T>C polymorphism and poorer clinical outcome with abiraterone for mCRPC patients. However, further validations on larger cohort of patients are needed to confirm its role as a predictive biomarker for abiraterone resistance.

Keywords CYP17A1 · Polymorphism · CRPC · Abiraterone · Pharmacogenetics

Introduction

Prostate cancer is the most commonly diagnosed cancer among men in Western countries, accounting for 24% of all new cancers diagnosed in 2018, and is considered as the second and third leading cause of cancer death in American and European men, respectively [1–3]. Although the incidence of prostate cancer is high, most of the cases are detected when the cancer is localised within the prostate, with a 5-year survival rate in USA of 98% [3]. The rate of patients with metastatic prostate cancer at diagnosis is less than 30% and remains low [4]. Metastatic prostate cancer may be present already as a disseminated disease at the time of diagnosis or as a disease recurrence after local therapy [5]. Androgen deprivation therapy (ADT) is the gold standard and the most effective initial treatment; however, after the initial response, almost all patients eventually progress following a median 18–24 months of ADT, to metastatic castration-resistant prostate cancer (mCRPC) [6, 7]. Despite the increasing options in terms of mCRPC treatment, median survival for mCRPC remains in the range of 15–36 months [6, 8]. Docetaxel was the gold standard for mCRPC treatment, being the first and only life prolonging agent until 2010 [5, 9]. However, in the last years, five new drugs have shown efficacy in improving overall survival in mCRPC

✉ Marzia Del Re
marzia.delre@gmail.com

[1] Unit of Clinical Pharmacology and Pharmacogenetics, Department of Clinical and Experimental Medicine, University Hospital of Pisa, 55, Via Roma, 56126 Pisa, Italy

[2] Unit of Medical Oncology, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy

patients. Cabazitaxel, abiraterone, enzalutamide, apalutamide, and radium-223 dichloride became, or will be in the near future, part of CRPC drugs armamentarium [10–12].

Abiraterone is a selective inhibitor of cytochrome P450 17-hydrolase (CYP17A1) [13, 14] and suppresses the androgen synthesis in adrenal glands, testicles and tumour microenvironment [15, 16]. Although phase III clinical trials demonstrated a clear improvement in progression-free survival (PFS) and overall survival (OS) in patients with mCRPC treated with abiraterone acetate plus prednisone [17, 18], the response to treatment is heterogeneous and about 25–30% of patients experience primary resistance. To date, few predictive biomarkers of efficacy have been identified in mCRPC patients and none of them has been investigated in prospective randomised trials to confirm its predictive role in clinical practice [19]. CYP17A1 is the direct target of abiraterone and, therefore, could be one of the most important biomarkers to predict therapy response/failure. CYP17A1 is located on chromosome 19q23.4, and catalyses key reactions in sex-steroid biosynthesis, mediating 17α-hydroxylase and 17,20-lyase activities [20]. In vitro study demonstrated that alterations of CYP17A1 activity may play a role in reducing response to treatment [21], and the intratumour overexpression of CYP17A1—detected in prostate cancer tissue biopsies from patients treated with abiraterone—suggests the enzyme upregulation as a key mechanism of resistance to therapy [22]. A published retrospective study demonstrated an association between CYP17A1 copy number variation and shorter PFS in mCRPC patients treated with abiraterone [23], while another study, published by Binder et al., evaluated the predictive role of 4 CYP17A1 single nucleotide polymorphisms (SNPs) (rs2486758, rs4919685, rs17115100 and rs743572) with respect to abiraterone response in 87 CRPC patients [24]. The study showed a relationship between the rs2486758 SNP (c.-362T > C), a worse biochemical response rate and a shorter time to biochemical progression [24]. However, conflicting results concerning any correlation between CYP17A1 polymorphisms and the anti-hormonal agent response have been reported [25]. The aim of the present study was to investigate the correlation between CYP17A1 c.-362T > C polymorphism with clinical outcome, verifying its impact on abiraterone efficacy.

Patients and methods

Patient selection

The study is a mono-institutional pharmacogenetic study that enrolled mCRPC patients receiving abiraterone acetate as per approved label. Inclusion criteria allowed the enrolment of patients with histologically or cytologically confirmed prostate adenocarcinoma, a castration-resistance state as defined per current clinical guidelines (castrate serum testosterone < 50 ng/dL or 1.7 nmol/L plus either biochemical progression, which consists in 3 consecutive rises in PSA 1 week apart resulting in two 50% increases over the nadir, and a PSA > 2 ng/mL or, radiological progression, that is, the appearance of new lesions on bone scan or CT scan), with documented metastases confirmed by CT and/or technetium-99 bone scan and/or 18F-fluorocholine PET-CT, and patients had to be eligible for receiving abiraterone acetate as per current clinical guidelines.

The study was approved by the Ethics Committee of Pisa University Hospital and conducted in accordance with the principles of the Declaration of Helsinki. All patients gave their signed informed consent before blood collection and data analysis.

Blood sample collection, DNA isolation, and SNP genotyping

Blood samples were collected in tubes containing EDTA and stored at − 80 °C until analysis. Genomic DNA was extracted from 200 µl of whole blood using QIAamp DNA Blood Mini kit (Qiagen, Valencia, CA) following the manufacturer's protocol. The analysis of the CYP17A1 SNP (rs2486758) c.-362T > C was conducted on a Quantstudio Dx (Applied Biosystem, Foster City, CA) by using the TaqMan® SNP Genotyping Assay (Assay ID: C__15807798_10) according to the manufacturer's standard protocol.

Statistical analysis

Categorical data were described by absolute and relative frequencies, whereas quantitative data were reported as mean and standard deviation. PFS was defined as the length of time from starting abiraterone treatment to radiological progression of disease or death. OS was defined as the length of time from starting abiraterone treatment to death for any cause. PSA-PFS was defined as the presence of two consecutive total serum PSA increases ≥ 50%, at least 2 weeks apart. The Kaplan–Meier method was used to create PFS curves and log-rank test was used to evaluate the differences between curves. Hazard ratio was calculated to compare cumulative risks. Univariate and multivariate analyses were performed to evaluate the correlation between clinical parameters and the CYP17A1 SNP. The frequency of CYP17A1 c.-362T>C polymorphism in our cohort was compared to the worldwide population and Hardy–Weinberg equilibrium was assessed. Allelic frequencies were determined by dbSNP short genetic variations. Statistical significance was defined by a p value of 0.05 or lower. Analyses were performed using MedCalc version 14.8.1.

Table 1 Patient characteristics

Baseline characteristics	N = 60
Age—median (range)	74 (54-86)
ECOG performance status, number (%)	
0	34 (56)
1	25 (42)
2	1 (2)
Tumour stage at diagnosis, number (%)	
T1/2 N0 M0	3 (5)
T3/4 N0 M0	15 (25)
Any T N1 M0	13 (22)
Any T any N M1	22 (36)
Unknown	7 (12)
Gleason score at diagnosis, number (%)	
≤ 7	23 (38)
> 7	33 (55)
Unknown	4 (7)
Presence of bone metastases	
No	11 (18)
Yes	49 (82)
Presence of lymph node metastases	
No	26 (43)
Yes	34 (57)
Presence of visceral (lung and/or liver) metastases	
No	17 (28)
Yes	43 (72)
Lung	1 (2)
Liver	5 (12)
Volume of disease at diagnosis (according to CHAARTED criteria)	
Low	42 (70)
High	14 (23)
Unk	4 (7)
High-/Low-risk according to LATITUDE criteria	
High	12 (20)
Low	48 (80)
No. of previous chemotherapeutic regimens (%)	
0	23 (38)
1	21 (35)
2	16 (27)
Baseline total PSA level (ng/mL), median (range)	25.32 (0.35–4581)

Results

The study included a total of 60 mCRPC patients treated between 2012 and 2019 at the University Hospital of Pisa (Italy), with abiraterone acetate plus prednisone as per clinical practice. The main characteristics of patients are reported in Table 1. The majority of patients had a good performance status (0–1, 98%), high Gleason score (≥ 7, 55%) and locally advanced (N1) or metastatic (M1) disease at diagnosis (58%). Twenty-three percent of patients had a high volume of disease at diagnosis of metastatic disease according to CHAARTED criteria [26] or a high-risk disease according to Latitude criteria [27].

After treatment with abiraterone acetate, the majority of patients (52%) received a subsequent chemotherapy regimen. In particular, 35% and 17% received docetaxel and cabazitaxel, respectively. Seven (11.7%) patients had a partial response (PR), 28 (46.7%) patients achieved a stable disease (SD), and 14 (23.3%) had a progressive disease (PD). In 11 patients (18.3%), it was not possible to assess tumour response. Median PFS on abiraterone treatment was 10.8 months (95% CI 7.9–13 months) and median OS was 21 months (95% CI 13–29.4 months).

The calculation of Hardy–Weinberg equilibrium was performed and the CYP17A1 polymorphism was found to be in equilibrium (Table 2). The association between CYP17A1 (rs2486758) c.-362T > C and PFS and OS was evaluated. PFS was longer in patients carrying the wild-type TT genotype compared to patients carrying at least one mutant allele TC/CC (median 14.2 vs 10.7 months, $p = 0.04$; Fig. 1a). The PSA-PFS was also longer in patients carrying the TT vs CT/CC genotypes (8 vs 16 months, $p = 0.04$) (Fig. 1b). A difference was observed in the OS analysis: median OS was 32 months for the TT genotype vs 21.6 months for the TC/CC genotypes, although it was not statistically significant ($p = 0.14$). No association was found between CYP17A1 c.-362T>C and biochemical response to abiraterone ($p > 0.05$).

Cox proportional hazard ratios were used to assess the effect of CYP17A1 c.-362T>C polymorphism on the prediction of time-to-event outcomes. In the univariate model, the polymorphism showed to significantly influence

Table 2 Allele and genotype frequencies of CYP17A1 SNP (*SNPs* single nucleotide polymorphisms, *N* number of patients)

SNP	Allele	Allele frequency		P value	Genotypes	Genotype frequency		HWE (p_{HWE})
		Case series	Population			Observed numbers	Expected numbers	
CYP17A1 c.-362T > C	T	71.7	78.7	0.323	TT	30	30.8	0.27 (0.60)
	C	28.3	21.3		CT	26	24.4	
					CC	4	4.8	

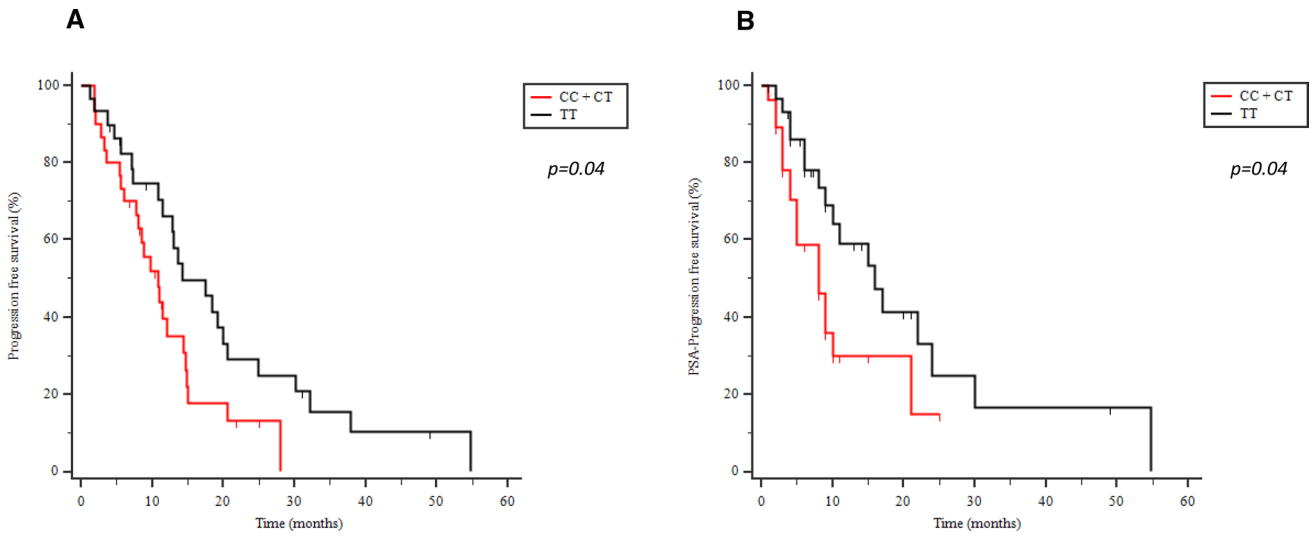

Fig. 1 **a, b** Kaplan–Meier curves for progression-free survival (PFS) (**a**) and PSA-progression-free survival (PSA-PFS) (**b**) in patients treated with abiraterone stratified by CYP17A1 c.-362T>C genotypes

abiraterone PFS (OR = 0.54, CI 95%, 0.29–0.99; $p = 0.04$), together with previous use of docetaxel (32/60 patients; OR = 2.23 CI 95%, 1.21–4.1; $p = 0.01$). Clinical characteristics of patients and known risk factors for disease progression, such as age, higher Gleason score (≤7, > 7) and high volume/high-risk metastatic disease at diagnosis, were also analysed (Table 3). In the multivariate model, only previous use of docetaxel was confirmed as an independent predictor of PFS (OR 2.17 CI 95%, 1.17–4.01; $p = 0.02$).

Biochemical or radiographic PFS to first-line taxane chemotherapy did not differ significantly depending on CYP17A1 c.-362T>C genotype ($p > 0.05$): median PFS was 6 months in patients carrying TC/CC genotypes (95% CI 4.03–6.30 months) and 5.9 months in patients carrying TT genotype (95% CI 5.03–7.7 months).

Discussion

Genotyping analysis of genes involved in prostate cancer carcinogenesis, progression and treatment could help us to better understand the behaviour of CRPC and, consequently, patient outcomes [28]. It has been demonstrated that epigenetic markers and genetic alterations are able to predict clinical outcome in CRPC patients treated with new hormonal therapy [29–31]. However, few studies have investigated the effect of polymorphisms on outcome prediction [19, 23, 25, 32], and the majority of published studies show conflicting results. Since CYP17 is involved in step regulation in the biosynthesis of testosterone and is, therefore, the target of abiraterone, its genetic characterisation could facilitate the understanding of patients'

Table 3 Univariate and multivariate analysis of clinical variables influencing PFS

Variable	Univariate		Multivariate	
	OR (95% CI)	*p* value	HR (95% CI)	*p*-value
Age (< 75, ≥ 75)	1.21 (0.68–2.16)	0.51	–	–
Gleason Score (≤ 7; > 7)	1.17 (0.62–2.19)	0.63	–	–
High-volume metastatic disease at diagnosis (yes; no)	1.01 (0.51–2.02)	0.97	–	–
High-risk metastatic disease at diagnosis (yes; no)	0.99 (0.49–1.98)	0.98	–	–
Prior use of docetaxel (yes; no)	2.23 (1.21–4.1)	0.01	2.17 (1.17–4.01)	0.02
CYP17A1 rs2486758 (TT; TC/CC)	0.54 (0.29–0.99)	0.04	0.58 (0.31–1.06)	0.08

response/resistance to abiraterone therapy. The present study evaluated the impact of the CYP17A1 c.-362T > C SNP (rs2486758) on clinical outcome in 60 mCRPC patients treated with abiraterone, showing a significant relationship between the mutant genotype and a shorter radiological PFS. In the multivariate analysis, prior use of docetaxel was confirmed as an independent predictor of PFS, accordingly to a previous study [9]. However, only 32 patients have been treated in first line with docetaxel, suggesting a possible limit of the study. Indeed, in the univariate model, CYP17A1 c.-362T>C polymorphism was shown to significantly influence abiraterone PFS, confirming its potential role in drug resistance.

Binder et al. already evaluated the predictive role of 4 CYP17A1 SNPs (rs2486758, rs4919685, rs17115100 and rs743572) and their association with response to the antihormonal agents in 87 mCRPC patients [24]. Of the analysed SNPs, only the c.-362T > C (rs2486758) was associated with a worse biochemical response rate to abiraterone and a shorter abiraterone biochemical progression [24]. These results highlight that germinal polymorphisms of target genes are likely to be included between the most important sources of individual variability in drug efficacy [33].

CYP17A1 overexpression suggested the enzyme upregulation as a key mechanism of resistance to hormonal therapy and its association with outcome (median PFS and OS) of mCRPC patients treated with abiraterone [22, 23, 32]. The c.-362T > C polymorphism represents a variant of the CYP17A1 gene located in the 5′ promoter region [34]. The minor C-allele seems to be associated with an increased expression of CYP17 gene, by affecting gene splicing and transcription factor binding or the sequence of noncoding RNA [35]. Abiraterone is a potent inhibitor of the steroidogenic enzyme CYP17A1 and its increased transcriptional activity in the presence of C allele may be associated with the mechanism of resistance, due to a decreased target occupancy and inhibition. Intriguingly, another work by Bremmer et al. showed that when androgen signalling is impaired, i.e. by RNA interference with androgen receptor (AR) expression by specific siRNA, the same resistance effect becomes evident [36]. Therefore, CYP17A1 upregulation is indicative for an androgen signalling impairment, which may be not limited to abiraterone treatment and may represent a negative feedback loop upon the same pathway [37]. Therefore, variations of key genes involved in androgen biosynthesis and metabolism have been also evaluated as candidate biomarkers for prostate cancer susceptibility. A possible association of c.-362T > C polymorphism with prostate cancer risk has been reported by Wang et al. [38]. Again, the hypothesis could lie in the CYP17A1 overexpression, which is able to increase the testosterone synthesis, allowing the risk of prostate cancer development. However, well-designed epidemiologic studies are necessary to confirm this association.

Even if the present study analysed only one selected SNP, with a high probability of being correlated with abiraterone activity [24], other polymorphisms in genes involved in steroidogenesis or drug metabolism are worth being evaluated, including TSPYL, which was previously shown to be associated with regulation of CYP17A1 and CYP3A4 expression [39]. Polymorphisms affecting SULT2A1 and CYP3A4 genes, involved in abiraterone metabolism, could be also evaluated to identify a possible influence in pharmacokinetics and drug exposure [40].

With the limitation of the retrospective nature of the study and the relatively small sample size, our analysis revealed a possible association between CYP17A1 c.-362T>C germinal polymorphism and abiraterone resistance, based on PFS and PSA-PFS.

We found no association with overall survival; however, such negative finding might be explained by the subsequent therapies that the vast majority of patients received. The administration of a chemotherapy regimen, which is unaffected by CYP17A1 alteration, might have mitigated the effect of this molecular characteristic on the final outcome. Indeed, it is necessary to validate this result in a larger and independent validation cohort. Moreover, the current approach to correlate PFS and PSA-PFS to a single SNP may be replaced by a comprehensive genetic analysis to evaluate the interaction between different SNPs (i.e. haplotype) and survival. Further studies of larger case series are needed to better investigate the therapeutic window of the drug and the potential impact of germinal SNPs.

Acknowledgements None.

Compliance with ethical standards

Conflict of interest :The authors declare no conflict of interest.

References

1. Epidemiology of prostate cancer in Europe [Internet]. European Commission (2015) https://ec.europa.eu/jrc/en/publication/epidemiology-prostate-cancer-europe
2. Arnold M, Karim-Kos HE, Coebergh JW, Byrnes G, Antilla A, Ferlay J, Renehan AG, Forman D, Soerjomataram I (2015) Recent trends in incidence of five common cancers in 26 European countries since 1988: analysis of the European Cancer Observatory. Eur J Cancer 51(9):1164–1187. https://doi.org/10.1016/j.ejca.2013.09.002
3. Siegel RL, Miller KD, Jemal A (2018) Cancer statistics. CA Cancer J Clin 68(1):7–30. https://doi.org/10.3322/caac.21442
4. Crawford ED, Petrylak D, Sartor O (2017) Navigating the evolving therapeutic landscape in advanced prostate cancer. Urol Oncol 35S:S1–S13. https://doi.org/10.1016/j.urolonc.2017.01.020

5. Dong L, Zieren RC, Xue W, de Reijke TM, Pienta KJ (2019) Metastatic prostate cancer remains incurable, why? Asian J Urol 6(1):26–41. https://doi.org/10.1016/j.ajur.2018.11.005
6. Kirby M, Hirst C, Crawford ED (2011) Characterising the castration-resistant prostate cancer population: a systematic review. Int J Clin Pract 65(11):1180–1192. https://doi.org/10.1111/j.1742-1241.2011.02799.x
7. Taylor BS, Schultz N, Hieronymus H, Gopalan A, Xiao Y, Carver BS, Arora VK, Kaushik P, Cerami E, Reva B, Antipin Y, Mitsiades N, Landers T, Dolgalev I, Major JE, Wilson M, Socci ND, Lash AE, Heguy A, Eastham JA, Scher HI, Reuter VE, Scardino PT, Sander C, Sawyers CL, Gerald WL (2010) Integrative genomic profiling of human prostate cancer. Cancer Cell 18(1):11–22. https://doi.org/10.1016/j.ccr.2010.05.026
8. Higano CS, Crawford ED (2011) New and emerging agents for the treatment of castration-resistant prostate cancer. Urol Oncol 29(6 Suppl):S1–8. https://doi.org/10.1016/j.urolonc.2011.08.013
9. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, Oudard S, Theodore C, James ND, Turesson I, Rosenthal MA, Eisenberger MA, Investigators TAX (2004) Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 351(15):1502–1512. https://doi.org/10.1056/NEJMoa040720
10. Nuhn P, De Bono JS, Fizazi K, Freedland SJ, Grilli M, Kantoff PW, Sonpavde G, Sternberg CN, Yegnasubramanian S, Antonarakis ES (2019) Update on systemic prostate cancer therapies: management of metastatic castration-resistant prostate cancer in the era of precision oncology. Eur Urol 75(1):88–99. https://doi.org/10.1016/j.eururo.2018.03.028
11. Sartor O, de Bono JS (2018) Metastatic Prostate Cancer. N Engl J Med 378(7):645–657. https://doi.org/10.1056/NEJMra1701695
12. Chong JT, Oh WK, Liaw BC (2018) Profile of apalutamide in the treatment of metastatic castration-resistant prostate cancer: evidence to date. Onco Targets Ther 11:2141–2147. https://doi.org/10.2147/OTT.S147168
13. O'Donnell A, Judson I, Dowsett M, Raynaud F, Dearnaley D, Mason M, Harland S, Robbins A, Halbert G, Nutley B, Jarman M (2004) Hormonal impact of the 17alpha-hydroxylase/C(17,20)-lyase inhibitor abiraterone acetate (CB7630) in patients with prostate cancer. Br J Cancer 90(12):2317–2325. https://doi.org/10.1038/sj.bjc.6601879
14. Attard G, Reid AH, Yap TA, Raynaud F, Dowsett M, Settatree S, Barrett M, Parker C, Martins V, Folkerd E, Clark J, Cooper CS, Kaye SB, Dearnaley D, Lee G, de Bono JS (2008) Phase I clinical trial of a selective inhibitor of CYP17, abiraterone acetate, confirms that castration-resistant prostate cancer commonly remains hormone driven. J Clin Oncol 26(28):4563–4571. https://doi.org/10.1200/JCO.2007.15.9749
15. Ferraldeschi R, Sharifi N, Auchus RJ, Attard G (2013) Molecular pathways: inhibiting steroid biosynthesis in prostate cancer. Clin Cancer Res 19(13):3353–3359. https://doi.org/10.1158/1078-0432.CCR-12-0931
16. Miller WL, Auchus RJ (2011) The molecular biology, biochemistry, and physiology of human steroidogenesis and its disorders. Endocr Rev 32(1):81–151. https://doi.org/10.1210/er.2010-0013
17. Ryan CJ, Smith MR, Fizazi K, Saad F, Mulders PF, Sternberg CN, Miller K, Logothetis CJ, Shore ND, Small EJ, Carles J, Flaig TW, Taplin ME, Higano CS, de Souza P, de Bono JS, Griffin TW, De Porre P, Yu MK, Park YC, Li J, Kheoh T, Naini V, Molina A, Rathkopf DE, Investigators C-A (2015) Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 16(2):152–160. https://doi.org/10.1016/S1470-2045(14)71205-7
18. Rydzewska LHM, Burdett S, Vale CL, Clarke NW, Fizazi K, Kheoh T, Mason MD, Miladinovic B, James ND, Parmar MKB, Spears MR, Sweeney CJ, Sydes MR, Tran N, Tierney JF, STA Collaborators (2017) Adding abiraterone to androgen deprivation therapy in men with metastatic hormone-sensitive prostate cancer: a systematic review and meta-analysis. Eur J Cancer 84:88–101. https://doi.org/10.1016/j.ejca.2017.07.003
19. Beltran H, Antonarakis ES, Morris MJ, Attard G (2016) Emerging molecular biomarkers in advanced prostate cancer: translation to the clinic. Am Soc Clin Oncol Educ Book 35:131–141. https://doi.org/10.14694/EDBK_159248
20. Waterman MR, Keeney DS (1992) Genes involved in androgen biosynthesis and the male phenotype. Horm Res 38(5–6):217–221. https://doi.org/10.1159/000182546
21. Mostaghel EA, Marck BT, Plymate SR, Vessella RL, Balk S, Matsumoto AM, Nelson PS, Montgomery RB (2011) Resistance to CYP17A1 inhibition with abiraterone in castration-resistant prostate cancer: induction of steroidogenesis and androgen receptor splice variants. Clin Cancer Res 17(18):5913–5925. https://doi.org/10.1158/1078-0432.CCR-11-0728
22. Cai C, Chen S, Ng P, Bubley GJ, Nelson PS, Mostaghel EA, Marck B, Matsumoto AM, Simon NI, Wang H, Chen S, Balk SP (2011) Intratumoral de novo steroid synthesis activates androgen receptor in castration-resistant prostate cancer and is upregulated by treatment with CYP17A1 inhibitors. Cancer Res 71(20):6503–6513. https://doi.org/10.1158/0008-5472.CAN-11-0532
23. Salvi S, Casadio V, Conteduca V, Burgio SL, Menna C, Bianchi E, Rossi L, Carretta E, Masini C, Amadori D, Calistri D, Attard G, De Giorgi U (2015) 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 112(10):1717–1724. https://doi.org/10.1038/bjc.2015.128
24. Binder M, Zhang BY, Hillman DW, Kohli R, Kohli T, Lee A, Kohli M (2016) Common genetic variation in CYP17A1 and response to abiraterone acetate in patients with metastatic castration-resistant prostate cancer. Int J Mol Sci. https://doi.org/10.3390/ijms17071097
25. Salvi S, Casadio V, Burgio SL, Conteduca V, Rossi L, Menna C, Carretta E, Costantini M, Zoli W, De Giorgi U (2016) CYP17A1 polymorphisms and clinical outcome of castration-resistant prostate cancer patients treated with abiraterone. Int J Biol Markers 31(3):e264–269. https://doi.org/10.5301/jbm.5000197
26. Sweeney CJ, Chen YH, Carducci M, Liu G, Jarrard DF, Eisenberger M, Wong YN, Hahn N, Kohli M, Cooney MM, Dreicer R, Vogelzang NJ, Picus J, Shevrin D, Hussain M, Garcia JA, DiPaola RS (2015) Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med 373(8):737–746. https://doi.org/10.1056/NEJMoa1503747
27. Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, Ozguroglu M, Ye D, Feyerabend S, Protheroe A, De Porre P, Kheoh T, Park YC, Todd MB, Chi KN, Investigators L (2017) Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med 377(4):352–360. https://doi.org/10.1056/NEJMoa1704174
28. Cozar JM, Robles-Fernandez I, Martinez-Gonzalez LJ, Pascual-Geler M, Rodriguez-Martinez A, Serrano MJ, Lorente JA, Alvarez-Cubero MJ (2018) Genetic markers a landscape in prostate cancer. Mutat Res 775:1–10. https://doi.org/10.1016/j.mrrev.2017.11.004
29. Hendriks RJ, Dijkstra S, Smit FP, Vandersmissen J, Van de Voorde H, Mulders PFA, van Oort IM, Van Criekinge W, Schalken JA (2018) Epigenetic markers in circulating cell-free DNA as prognostic markers for survival of castration-resistant prostate

cancer patients. Prostate 78(5):336–342. https://doi.org/10.1002/pros.23477
30. Seisen T, Roupret M, Gomez F, Malouf GG, Shariat SF, Peyronnet B, Spano JP, Cancel-Tassin G, Cussenot O (2016) A comprehensive review of genomic landscape, biomarkers and treatment sequencing in castration-resistant prostate cancer. Cancer Treat Rev 48:25–33. https://doi.org/10.1016/j.ctrv.2016.06.005
31. Del Re M, Crucitta S, Restante G, Rofi E, Arrigoni E, Biasco E, Sbrana A, Coppi E, Galli L, Bracarda S, Santini D, Danesi R (2018) Pharmacogenetics of androgen signaling in prostate cancer: focus on castration resistance and predictive biomarkers of response to treatment. Crit Rev Oncol Hematol 125:51–59. https://doi.org/10.1016/j.critrevonc.2018.03.002
32. Zhang B, Binder M, Costello B, Quevedo F, Kohli M (2016) Association of CYP17A1 single nucleotide polymorphism (SNP) with response to abiraterone acetate (AA) in metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol 34:e16603–e16603. https://doi.org/10.1200/JCO.2016.34.15_suppl.e16603
33. Roden DM, Wilke RA, Kroemer HK, Stein CM (2011) Pharmacogenomics: the genetics of variable drug responses. Circulation 123(15):1661–1670. https://doi.org/10.1161/CIRCULATIONAHA.109.914820
34. Diver LA, MacKenzie SM, Fraser R, McManus F, Freel EM, Alvarez-Madrazo S, McClure JD, Friel EC, Hanley NA, Dominiczak AF, Caulfield MJ, Munroe PB, Connell JM, Davies E (2016) Common polymorphisms at the CYP17A1 locus associate with steroid phenotype: support for blood pressure genome-wide association study signals at this locus. Hypertension 67(4):724–732. https://doi.org/10.1161/HYPERTENSIONAHA.115.06925
35. Manolio TA (2010) Genomewide association studies and assessment of the risk of disease. N Engl J Med 363(2):166–176. https://doi.org/10.1056/NEJMra0905980
36. Bremmer F, Jarry H, Strauss A, Behnes CL, Trojan L, Thelen P (2014) Increased expression of CYP17A1 indicates an effective targeting of the androgen receptor axis in castration resistant prostate cancer (CRPC). Springerplus 3:574. https://doi.org/10.1186/2193-1801-3-574
37. Auchus ML, Auchus RJ (2012) Human steroid biosynthesis for the oncologist. J Investig Med 60(2):495–503. https://doi.org/10.2310/JIM.0b013e3182408567
38. Wang F, Zou YF, Feng XL, Su H, Huang F (2011) CYP17 gene polymorphisms and prostate cancer risk: a meta-analysis based on 38 independent studies. Prostate 71(11):1167–1177. https://doi.org/10.1002/pros.21332
39. Qin S, Liu D, Kohli M, Wang L, Vedell PT, Hillman DW, Niu N, Yu J, Weinshilboum RM, Wang L (2018) TSPYL family regulates CYP17A1 and CYP3A4 expression: potential mechanism contributing to abiraterone response in metastatic castration-resistant prostate cancer. Clin Pharmacol Ther 104(1):201–210. https://doi.org/10.1002/cpt.907
40. Benoist GE, Hendriks RJ, Mulders PF, Gerritsen WR, Somford DM, Schalken JA, van Oort IM, Burger DM, van Erp NP (2016) Pharmacokinetic aspects of the two novel oral drugs used for metastatic castration-resistant prostate cancer: abiraterone acetate and enzalutamide. Clin Pharmacokinet 55(11):1369–1380. https://doi.org/10.1007/s40262-016-0403-6