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Androgen receptor variant 7 (AR-V7) in sequencing therapeutic agents for castration resistant prostate cancer

A critical review

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Abstract

Background: androgen receptor variant 7 (AR-V7) has been suggested as potential marker for treatment selection in men with metastatic castration-resistant prostate cancer (mCRPC). The aim of the present review is to critically analyze: frequency of the AR-V7 expression in mCRPC cases—impact of AR-V7 expression on abiraterone, enzalutamide, and taxane therapy.

Methods: we searched in the Medline and Cochrane Library database from the literature of the past 10 years. We critically evaluated the level of evidence according to the European Association of Urology (EAU) guidelines.

Results: 12 clinical trials were selected. The determination of AR-V7 in peripheral blood using circulating tumor cells mRNA seems to be the preferred method. At baseline, the mean percentage of cases with AR-V7 positivity was 18.3% (range 17.8%–28.8%). All data on mCRPC submitted to enzalutamide or abiraterone reported a significantly ($P < .05$) lower clinical progression-free survival (CPFS) and overall survival (OS) in AR-V7+ than AR-V7− cases (CPFS hazard ratio [HR]: 2.3; 95% CI 1.1–4.9; OS HR: 3.0; 95% CI 1.4–6.3). In mCRPC cases submitted to chemotherapies data are not homogeneous and some studies showed no association between CPFS or OS and AR-V7 status (OS HR 1.6; 95% CI 0.6–4.4; $P = .40$).

Conclusions: the suggestion is that taxane therapy is more efficacious than abiraterone or enzalutamide for men with AR-V7+ CRPC. On the contrary, clinical outcomes did not seem to differ significantly on the basis of the type of therapy used among AR-V7− cases.

Abbreviations: ADT = androgen deprivation therapies, AR = androgen receptor, AR-V7 = androgen receptor variant 7, CPFS = clinical progression free survival, CRPC = castration resistant prostate cancer, HR = hazard ratio, mCRPC = metastatic castration resistant prostate cancer, OS = overall survival, PC = prostate cancer, PCR = polymerase chain reaction, PSA = prostate specific antigen.

Keywords: abiraterone, androgen receptor, castration resistant, enzalutamide, prostate neoplasm, taxane

1. Introduction: the clinical point

Prostate cancer (PC) is an androgen-dependent disease and androgen receptor (AR) is one of the main molecular targets for systemic therapy. After an initial response to first-line androgen deprivation therapies (ADT), nearly all cases with advanced PC progress to a castration-resistant prostate cancer (CRPC). In CRPC, however, AR continues to be a primary molecular driver, as evidenced by significant response to novel hormonal therapies, abiraterone, and enzalutamide.[1] Mechanisms of resistance to systemic therapies in PC are also driven by AR aberrations or overexpression, AR gene amplification, and mutations, AR variants (AR-Vs).[2]

AR-Vs are truncated AR proteins without the AR ligand-binding domain, allowing for constitutive AR signaling in the absence of androgens. A structural rearrangement in AR gene and alternative AR mRNA splicing are 2 possible mechanisms for the development of AR-Vs in CRPC.[3] Since their discovery in 2004, the role of AR-Vs has remained enigmatic.[4] Their possible clinical utility was demonstrated in 2014 by Antonarakis et al[5] who noted an association between androgen receptor variant 7 (AR-V7) in circulating tumor cells (CTC) and outcomes in PC cases treated with second-generation androgen signaling inhibitors.

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The manuscript does not directly contain clinical studies or patient data but is a critical review on already published clinical trials.

The authors declare that they have no conflict of interest

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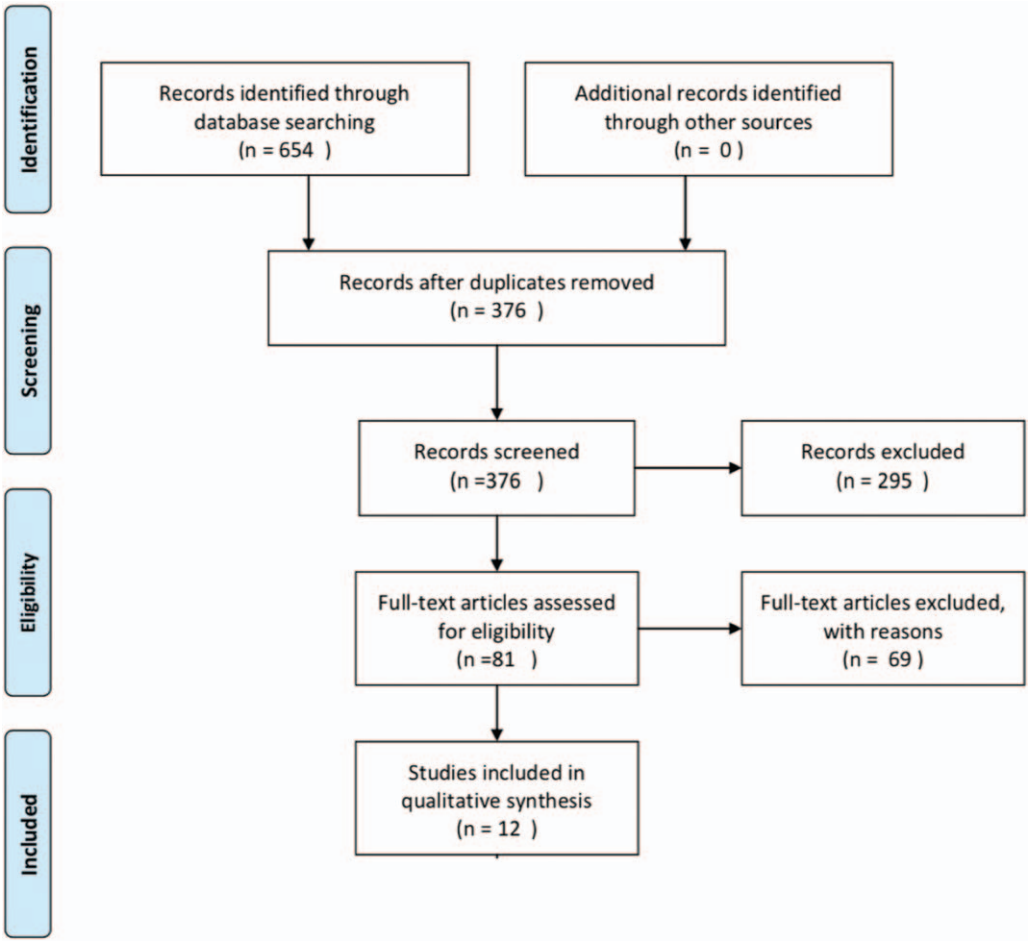

Figure 1. PRISMA diagram for study selection.

Multiple AR-Vs have been characterized (Fig. 1). To date, AR-V7 has been studied in greatest detail and it has been suggested as potentially clinical marker for treatment selection in men with CRPC.[6] Prior studies have determined that AR-Vs can be detected at the RNA and protein levels in tissue samples. Although AR-Vs can be detected in untreated PC and in benign prostate tissue, their levels are lower and cannot lead to robust evaluation by RNA in situ hybridization or immunohistochemistry. AR-V7 expression is significantly higher in CRPC, due to AR gene amplification and induction by ADT.[7]

Other studies have utilized CTC, plasma exosomes and also whole blood samples for the detection of AR-V7 in men with metastatic castration-resistant prostate cancer (mCRPC).[8] There are 2 clinically available CTC-based AR-V7 tests: one uses a polymerase chain reaction (PCR) in a capture-based CTC system and the second applies an immunofluorescent protein assay.[4] Each of these AR-V7 testing has its limitations and a significant proportion of CRPC cases are CTC negative. The St. Gallen PC conference reached a consensus against the use of AR-V7 in routine practice for mCRPC.[3] However, a recent clinical audit by the Johns Hopkins revealed that the determination of AR-V7 status influenced clinical decision making in a significant proportion of CRPC patients.[9] The results for an AR-V7- test did not change the clinical practice of the providers, whether almost two-thirds (62%) of AR-V7+ tests resulted in a change in management.[9] Patients with an AR-V7− result were preferentially treated with abiraterone or enzalutamide whereas after an AR-V7+ result, most cases shifted from abiraterone or enzalutamide to taxane chemotherapy (Fig. 2).

The optimal sequencing of therapeutic agents in mCRPC remains a major challenge. The analysis of AR-V7 as biomarker of therapeutic agents' resistance may help in this treatment decision and it may have a clinical and economic benefit. The National Comprehensive Cancer Network PC guidelines now suggest that AR-V7 testing can be used to define therapy selection in mCRPC, but this suggestion is not traduced as a recommended test.

2. Aim and methods

The aim of the present review is to critically analyze and compare the current evidence on the AR-V7 determination as prognostic clinical indicator of therapeutic response in mCRPC cases. In particular, we analyzed—frequency of the AR-V7 expression in mCRPC cases—impact of AR-V7 expression on abiraterone and enzalutamide therapy—impact of AR-V7 expression on taxane chemotherapy.

2.1. Evidence acquisition

We focused our analysis only on AR-V7 and not on all AR-Vs testing. We searched in the Medline and Cochrane Library database (primary fields: castration-resistant prostate neoplasm,

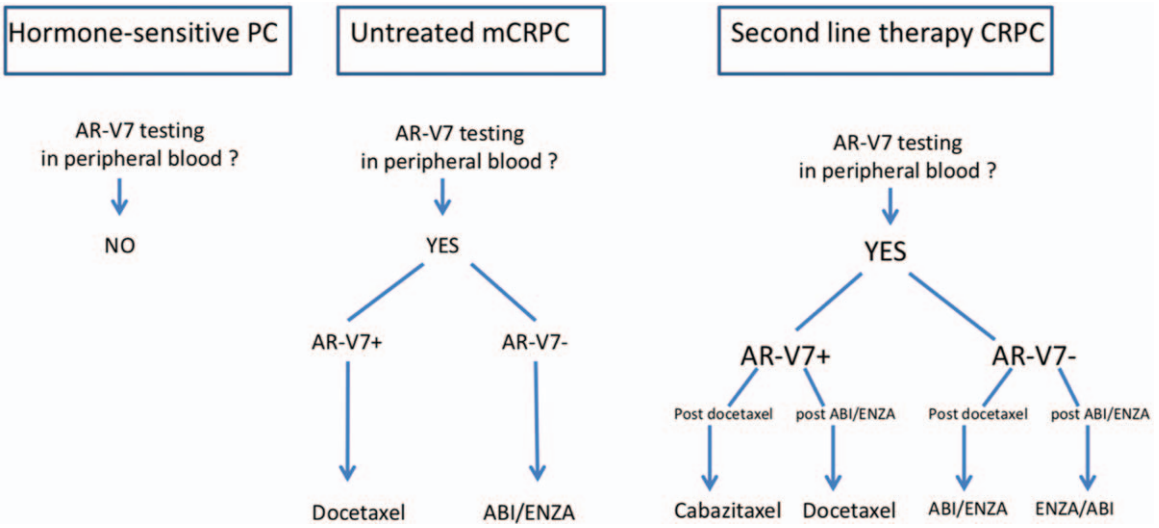

Figure 2. Potential decision algorithm on the basis of AR-V7 expression in mCRPC patients.

AND AR-V7 determination; secondary fields: abiraterone, enzalutamide, chemotherapy) without language restriction from the literature of the past 10 years, according to PRISMA guidelines (Fig. 1). Original and review articles were included and critically evaluated. Additional references were identified from reference lists of these articles. We have not included abstracts and reports from meetings. We analyzed data only from clinical trials (retrospective or prospective) focusing their attention on the clinical role of AR-V7 in PC.

For all studies, we critically evaluated the level of evidence according to the European Association of Urology (EAU) guidelines.[10]

3. Results

3.1. Search results

The database searches initially yielded 654 journal article references. Of these 573 were subsequently removed due to either duplication or a failure to meet the selection criteria. Full-text articles were then re-evaluated and critically analyzed for the remaining 81 journal references. Of these, 69 did not meet the inclusion criteria. The remaining 12 studies were considered for our critical review (Table 1).

3.1.1. Study location and type. The 12 studies[5,11–21] entered into the review, 4 were conducted in Europe,[11,13,17,18] 7 in US,[5,14–16,19–21] 1 in Canada[12] e 1 in China [20 either in China or US]. One study was multicenter randomized,[13] 8 were prospective mono or multicentric[5,11,12,14–16,18,19] and 3 were retrospective mono or multicentric studies.[17,20,21] Moreover, 5 studies comparatively considered the different treatments for PC [new hormone therapies versus chemotherapy: 15,16,19; abiraterone vs enzalutamide: 5,21; and 7 studies analyzed only 1 treatment[11–14,17,18,20] (Table 1).

3.1.2. Study sample sizes and cancer treatment. The sample size strongly varied from 21 to 401 cases analyzed in a single study. The total sample size of the 12 studies was 1629 (Table 1).

New hormone therapies such as Abiraterone or enzalutamide were used in 9 studies[5,11,12,14–17,19,21] with a total sample of 809 cases. Chemotherapies (taxane or cabazitaxel) were used in 4 studies[13,15,16,19] with a total sample of 210 cases.

3.1.3. Participant age. The range of mean age across the studies was very similar and it varied from 66.0 to 71.0 years. Also, the mean age of each treatment was similar with 68.5 years (SD ± 2.1) for new hormone therapies and 68.2 years (SD ± 1.7) for chemotherapies group (Table 1).

3.1.4. Cancer staging and follow-up. Ten out of 12 studies included only mCRPC cases (total cases: 957). Two studies considered hormone sensitive PC (total cases: 610); in particular one[18] considered M0 hormone sensitive cases stratified in terms of high risk versus low or intermediate risk submitted to androgen deprivation therapies and one[19] included all stages (M0-M1) (Table 1). Mean follow-up ranges from 7 to 140 months

3.1.5. AR-V7 analysis. Two studies[11,21] analyzed AR-V7 mRNA in peripheral blood considering high versus low expression. Eight studies[5,12,13–17,19] evaluated AR-V7 positivity in CTC mRNA from peripheral blood. Two studies[18,20] analyzed AR-V7 at tissue level by RT-PCR[18] or by immunohistochemistry[20] (Table 1).

3.2. Incidence of AR-V7 positivity in the studies

All studies[5,11–21] reported the level of AR-V7 positivity in the population analyzed. Independently to the method used, at baseline, before the beginning of specific treatments for CRPC, the mean percentage of cases (treated with androgen deprivation therapies for hormone-sensitive PC) with AR-V7 positivity was 18.3% (range 17.8%–28.8%).[5,11,14–20] A higher percentage of AR-V7 positivity was found by Onstenk et al[13] (55.0%) and by Qu et al[21] (95.0%), but their populations were already treated with abiraterone or enzalutamide.

3.2.1. Critical analysis and level of evidences. Data have been analyzed by several prospective multi or mono-center studies. From these data we can expect that, at baseline, a population with mCRPC, before the beginning of specific treatments (abiraterone, enzalutamide or chemotherapies) will show a 18% positivity for AR-V7 (level of evidence 2a). This percentage

Table 1

Main data from the 12 studies considered in the review.

Author (reference)	Location	Journal (year)	Study type	Treatment considered	Sample size	Participant mean age (years)(range)	PC stage	Site of Metastases	Main Results	ARV7 analysis type	End-points considered	Follow-Up mean months (range)
Setz AK et al.[11]	EU	Eur Urol 2017	Prospective mono-center	Enzalutamide or abiraterone	85 (total) 56 ABI 29 ENZA	71.0 (66–74)	mCRPC	96% bone 28% visceral	18% high AR-V7 PSA response 0% in AR-V7 high and 50% in AR-V7 low PSA-PFS 2.4 months (95% CI: 1.8–3.0) in high AR-V7 and 3.7 months (95% CI: 2.3–3.1) in low AR-V7 ($P<.001$) HR (high versus low): 7.0 (95% CI: 2.3–20.7) for PFS; 2.3 (95% CI: 1.1–4.9) for CPFS; 3.0 (95% CI: 1.4–6.3) for OS ($P<.001$)	Peripheral blood mRNA AR-V7 high if > 0.6% expression	% AR-V7 high PSA-PFS, CPFS, OS	20 .0
Todenhofer T et al[12]	Canada	J. Urol 2017	Prospective multi-center	Abiraterone	37	70.0 (53–87)	mCRPC	100% bone 8.1% visceral	CTC +: 137.5 (range 135–140) in AR-V7+ and 2 (range 0–90) in AR-V7 – ($P=.02$) PSA response: 0% in AR-V7+ and 41.9% in AR-V7-. OR 6.5 (95% CI:0.32–132.5) ($P=.27$) OS median: 6.6 months in AR-V7+ and 22.1 months in AR-V7- ($P=.004$)	Peripheral blood mRNA + CTC	% AR-V7 + PSA-PFS OS	21.0
Onstenk W et al[13]	EU	Eur Urol 2015	Multi-centre prospective randomized	Cabazitaxel	29	70.0	mCRPC	n.r.	55% AR-V7 + (pre-treated with ABI) PFS: HR (AR-V7+ versus AR-V7 -) 0.8 (95% CI: 0.4–1.8) $P=.6$ OS: HR (AR-V7+ versus AR-V/-) 1.6 (95% CI: 0.6–4.4) $P=.4$ no association with AR-V7 status	CTC > 3 mRNA from peripheral blood	% AR-V7 + PFS, OS	7.0 (2–27)
Antonarakis ES et al[14]	US	J Clin Oncol 2017	Prospective mono-centrer	Enzalutamide or abiraterone	202 (total) 95 ABI 107 ENZA	70.0	mCRPC	83% bone; 27% visceral	CTC –: 26.2%; CTC+ and AR-V7-: 56%; CTC+ and AR-V7 +: 17.8%. PSA response: 75.5% in CTC-, 52.2% in CTC- and AR-V7 -; 13.9% in CTC+ and AR-V7+($P<.01$). PSA-PFS: 11.3 months (95% CI: 8.7–13.8) in CTC-; 6.2months (95% CI: 5.8–7.3) in CTC+ and AR-V7 -; 2.1 months(95% CI: 1.9–3.1) in CTC+ and AR-V7 + ($P<.001$) CPFS: 13.9 months (95% CI: 11.0- not reached) in CTC -; 7.7 months (95% CI: 6.2–11.0) in CTC+ and AR-V7-; 3.1 months (95% CI: 2.3–3.7) in CTC+ and AR-V7+ ($P<.001$) OS: 28.7 months (95% CI: 28.4 - not reached) in CTC-; 29.5 months (95% CI: 18.4- not reached) in CTC+ and AR-V7 -; 11.2 months (95% CI: 8.3–17.1) in CTC+ and AR-V7+ ($P<.001$)	CTC mRNA from peripheral blood	% AR-V7 + PFS,OS	21.7
Scher HI et al[15]	US	JAMA Oncol 2016	Prospective multi-centrer	Abiraterone, enzalutamide, taxane	161(total)	68.0 (45–91)	mCRPC	84% bone; 38% visceral	18% AR-V7 + - submitted to ABI or Enza: CPFS: 2.3 months in AR-V7+ and 14.5 months in AR-V7 – ($P<.001$); OS: 4.6 in AR-V7+ and not reached in AR-V7 – ($P<.01$); HR 11.45 (95% CI: 5.6–23.8) $P<.001$ - submitted to taxane: CPFS 5.3 months in AR-V7 + and 6.6 months in AR-V7 – (P .46); OS: 8.9 months in AR-V7 + and 19.8months in AR-V7 - ($P<.001$); HR 3.74 (95%CI: 1.9–7.2) ($P<.001$) HR: response to taxane versus ABI or ENZA: 0.24 (95%CI: 0.10–0.57) ($P=.035$) in AR V7 + and 0.92 (95%CI: 0.44–1.95)($P>.05$) in AR-V7-	CTC mRNA from peripheral blood	% AR-V7+ PFS, OS	24.0
Scher HI et al[16]	US	Eur Urol 2017	prospective multi-centrer	Abiraterone, enzalutamide, taxane	191(total) 128 ABI or ENZA 63 Taxane	68.0 (45–91)	mCRPC	n.r.	18% AR-V7 + OS: HR (AR-V7 + versus AR-V7 -) 10.39 (95% CI: 2.1–51.4)($P<.001$) OS in only taxane group: HR 3.1 (95% CI: 1.4–7.0) ($P=.0004$)	CTC mRNA from peripheral blood	% AR-V7 + OS	25.0

(*continued*)

Table 1

(continued).

Author (reference)	Location	Journal (year)	Study type	Treatment considered	Sample size	Participant mean age (years)(range)	PC stage	Site of Metastases	Main Results	ARV7 analysis type	End-points considered	Follow-Up mean months (range)
									OS median only in taxane: 8.9 months in AR-V7+ and 9.2 months in AR-V7- OS median in AR-V7 +: 8.9 months median in taxane group and 4.6 months in ABI or ENZA group. HR for AR-V7 + (taxane versus ABI or Enza): 0.24 (95% CI: 0.07–0.7) (*P*=.019)			
Bernemann C et al[17]	EU	Eur Urol 2017	Retrospective mono-centrer	Abiraterone or enzalutamide	21 (total)	n.r.	mCRPC	n.r.	21 AR-V7 positive cases: 28.5% experienced response from ABI or ENZA with PFS median 2.9 months	CTC mRNA in peripheral blood	PFS in AR V7 positive cases	12.0
Chen X et al[18]	EU	Urol Oncol 2018	Prospective multi-centrer	Androgen deprivation therapies	401 (total) Group 1:163 Group 2: 238	n.r.	- Group 1:High risk after RP or RT Yes ADT - Group 2: Low or intermediate risk after RP No ADT	M0- hormone sensitive	- Group 1: High AR-V7 expression (TIS>2) 28.8% cases, either at primary tumor or lymph-node level. PSA-PFS:50.2 months in AR-V7 high versus median not reached in AR-V7 low (*P*=.015) HR 1.778 (95% CI: 1.113–2.841);(*P*=.016). - Group 2, 39.9% cases with AR-V7 high. No differences in PSA-PFSI between AR-V7 high and low (*P* .407); HR 1.29; 95% CI: 0.704–2.369; (*P*=.409) - In cases group 1 submitted to adjuvant HT, median PSA-PFS 10.7 months in AR-V7 high and 71 months in AR-V7 low (*P*=.002)	From tissue samples mRNA- (RT-PCR)	AR-V7 expression PSA-PFS	140.0
Antonarakis ES et al[19]	US	JAMA 2015	Prospective mono-centrer	Taxane or cabazitaxel versus Abiraterone or Enzalutamide	99 AR-V7 + (total) 37 treated with CHT 62 treated with ENZA or ABI	67.0 (46–82)	mCRPC	Bone 95% Visceral 35%	- CHT group: PSA response in 41% (95% CI: 18–67%) in AR-V7 + and 65% (95% CI: 41–85%) in AR-V7 – cases (*P* 0.19). PSA PFS: 4.5 months in AR-V7 + and 6.2 months in AR-V7 -. HR 2.1 (95% CI: 0.9–4.9; *P*=.06). CPFS: 5.1 months in AR-V7 + and 6.9 months in AR-V7 -. HR 2.8 (95% CI 1.2–6.9; *P* .02) OS: 9.2 months in AR-V7 + and 14.7 months in AR-V7 -. HR 2.5 (95% CI: 0.8–8.1; *P*=.11). - ABI or ENZA group: PSA response 0% in AR-V7 + and 64% in AR-V7 -. (*P*<.001 in comparison with CHT group for AR-V7 + and *P* .60 in ARV7-) - PFS CHT versus ABI or ENZA: HR 0.26 (95% CI: 0.11–0.59; *P*=.001) in AR-V7 + and HR 1.68 (95% CI: 0.84–3.33; *P*=.14) in AR-V7 – - OS in CHT vs ABI or ENZA: HR:0.83 (95% CI: 0.34–2.0; *P*=.76) in AR-V7 + and HR 1.55 (95% CI: 0.49–4.95; *P*=.46) in AR-V7 -	CTC mRNA peripheral blood	AR-V7% PSA response. PSA- PFS. CPFS; OS	7.7 (0.7–19.0)
Li H et al[20]	China and US	Modern Pathol 2018	Retrospective multi-center	primary androgen deprivation therapy	209	71.0 (53–96)	All stages hormone-sensitive	M0 and M1	19% AR-V7 +. PSA response 41% in AR-V7 + and 82% in AR-V7 – (*P*<.001). Median time for CRPC: 12 months (6–26) in AR-V7 + and 25 months (5–82) in AR-V7 – (*P*<.001). 2- year cumulative incidence CRPC: 88% (95% CI: 75–100%) in AR-V7 + and 28% (95% CI: 20–36%) in AR-V7 – (*P*<.001).	AR-V7 at tissue level immunohistochemistry	AR-V7%, PSA response and risk CRPC	80.0
Antonarakis ES et al[5]	US	N Engl J Med 2014	Prospective multi-centrer	Enzalutamide or abiraterone	62 (total) 31 ENZA 31 ABI	66.1	mCRPC	n.r.	PC deaths: 44% in AR-V7 + and 22% in AR-V7 - ENZA: AR-V7 + in 39% ABI: AR-V7 + in 19% - ENZA: PSA response 0% (95% CI: 0–26) in AR-V7 + and 53% (95% CI: 29–76) in AR-V7- (*P*.004). PSA- PFS: 1.4 months (95% CI: 0.9 – not reached) in AR-V7 + and 6.0 months (95% CI: 3.8- not reached) in AR-V7 –. HR 7.4 (95% CI: 2.7–20.6),	CTC mRNA from peripheral blood	AR-V7% PSA- PFS, CPFS, OS	9.0

(*continued*)

Table 1

(continued).

Author (reference)	Location	Journal (year)	Study type	Treatment considered	Sample size	Participant mean age (years)(range)	PC stage	Site of Metastases	Main Results	ARV7 analysis type	End-points considered	Follow-Up mean months (range)
									(*P*<.001). CPFS: 2.1 months (95% CI: 2.0 – not reached) in AR-V7 + and 6.1 months (95% CI: 4.7- not reached) in AR-V7 -; HR 8.5 (95% CI: 2.8–25.5; *P*<.001) OS: 5.5 months in AR-V7 + and not reached in AR-V7-. HR 6.9 (95% CI: 1.7–28.1 *P*=.002) - ABI: PSA response 0% (95% CI: 0–46) in AR-V7 + and 68% (95% CI: 46–85) in AR-V7 – (*P*=.004) PSA- PFS: 1.3 months (95% CI: 0.9- not reached) in AR-V7 + and 5.3 months (95% CI: 5.3- not reached) in AR-V7 -; HR 16.1 (95% CI: 3.9–66.0; *P*<.001) CPFS: 2.3 months (95% CI: 1.4- not reached) in AR-V7 + and 6.3 months (95% CI: 6.3- not reached) in AR-V7 -; HR 16.5 (95% CI: 3.3 – 82.9; *P*<.001) OS: 10.6 months in AR-V7+ and not reached in AR-V7-; HR 12.7 (95% CI: 1.3–125.3; *P* .006)			
Qu F et al[21]	US	Clin Cancer Res 2017	Retrospective mono-centrer	Abiraterone or Enzalutamide	132 (total) 81 ABI 51 ENZA	68.0 (46–89) in ABI and 68.5 (50–88) in ENZA	mCRPC	n.r.	AR-V7 + in 95% cases pre-treated with ABI and ENZA. AR-V7 high (> 19 copies/ugRNA) in 32% in ABI and 35.3% in ENZA - ABI: TTF: 8 months (4.2–12.1) in AR-V7 high and 15.6 months (8.1–21.3) in AR-V7 low (*P*=.046). HR: 1.31 (95% CI: 0.74–2.32)(*P*=.353) OS: 27.2months in AR-V7 high and 35.6 months in AR-V7 low (*P*>.05) - ENZA: TTF: 3.6 months(0.9–5.1) in AR-V7 high and 5.6 months (2.9–13.4) in AR-V7 low (*P*=.05). HR: 2.02 (95% CI: 1.0–4.0) (*P* .048). OS: 13.8 months in AR-V7 high and 29.1 months in AR-V7 low (*P*>.05)	AR-V7 RNA in peripheral blood	AR-V7%; TTF; OS	29.7 (3.6–47.5) in ABI and 23.9 (0.9–48.3) in ENZA

ABI = abiraterone, ADT = androgen deprivation therapy, CHT = chemotherapies, CPFS = clinical progression free survival, CTC = circulating tumour cells, ENZA = enzalutamide, n.r. = not reported, OS = overall survival, PSA-PFS = PSA progression free survival, TTF = time to treatment failure.

is very homogeneous among the studies and it is not influenced by the method used for AR-V7 analysis. Unfortunately, studies did not specify the type and the number of androgen deprivation therapies used in the hormone-sensitive phase or the Gleason score of these PC cases.

On the contrary in a population of mCRPC already treated with abiraterone or enzalutamide, we can expect higher percentage (>50%) of AR-V7 positivity (level of evidence 1b).

3.3. Impact of AR-V7 expression on prostate-specific antigen (PSA) response among the different treatment groups

The impact of AR-V7 positivity on PSA response (defined as PSA reduction >50%) was specifically evaluated in 6 studies.[5,11,12,14,19,20]

Li et al[20] retrospectively analyzed 209 cases with hormone-sensitive PC submitted to primary androgen deprivation therapy (M0 and M1 cases). PSA response during the follow-up was significantly ($P<.001$) influenced by AR-V7 status with lower percentage of response in AR-V7 positive cases (AR-V7+: 41%; AR-V7−: 82%).

In mCRPC cases submitted to abiraterone or enzalutamide,[5,11,12,14,19] homogeneously an AR-V7 positivity was associated with 0% of PSA responses versus a mean of 54.8% (range: 41.9%–64.0%) in AR-V7 negative cases ($P<.001$).

A prospective comparative study on mCRPC submitted to chemotherapies versus abiraterone or enzalutamide[19] showed that no significant differences ($P=.19$) in PSA response between AR-V7 positive (41.0%) and negative (65.0%) cases was reported in chemotherapies treated cases.

3.3.1. Critical analysis and level of evidences. The analysis of PSA response in hormone-sensitive PC cases was performed by only 1 retrospective study without stratification of cases on the basis of the lines of ADT used (level of evidence 2b). Different prospective studies well confirmed that mCRPC AR-V7 positive cases do not show a PSA response if treated either with abiraterone or enzalutamide (level of evidence 2a). Generally, stratified or comparative data between enzalutamide and abiraterone are not presented. On the contrary, a prospective comparative study showed that a significant percentage of AR-V7 positive cases show a PSA response if treated with chemotherapies (level of evidence 2b).

In conclusion, in the AR-V7+ mCRPC patients, PSA response, even if commonly considered as a secondary outcome compared with clinical progression or overall survival (OS), was found to be significantly influenced by Abiraterone or Enzalutamide therapy, while showed no response correlation in the group treated with taxane therapy. Data regarding this aspect cannot, however, be considered definitive in order to asses PSA response as a downstream target of the treatment regimen implemented.

3.4. Impact of AR-V7 expression on survival parameters among the different treatment groups

The impact of AR-V7 expression on PSA progression-free survival (PSA-PFS) was specifically examined in 7 studies.[5,11–14,18,19] All studies on mCRPC treated with abiraterone or enzalutamide[5,11,12,14,19] showed significantly ($P<.05$) lower PSA-PFS in AR-V7 positive (mean 1.8 months, range 1.3–2.4 months) than in AR-V7 negative (mean 5.3 months, range 3.7–6.2 months) (hazard ratio [HR] 7.4;95% CI 2.7–20.6) cases. On the contrary, in mCRPC cases submitted to chemotherapies,[13,19] PSA-PFS did not significantly vary according to AR-V7 status (HR0.8; 95% CI 0.4–1.8; $P=.60$). Also, in hormones sensitive cases,[18] PSA –PFS did not significantly vary according to AR-V7 (HR 1.29; 95% CI 0.7–2.3; $P=.409$).

The impact of AR-V7 expression on clinical progression-free survival (CPFS) and OS was evaluated in 9 studies.[5,11–16,19,21] All data on mCRPC submitted to enzalutamide or abiraterone[5,11–16,19,21] reported a significantly ($P<.05$) lower CPFS and OS in AR-V7 positive than in AR-V7 negative cases (mean CPFS: AR-V7+ 2.9 months; AR-V7− 8.3 months; mean OS: AR-V7+ 7.6 months; AR-V7− 22.1 months) (CPFS HR: 2.3;95% CI 1.1–4.9; OS HR: 3.0; 95% CI 1.4–6.3). In mCRPC cases submitted to chemotherapies,[13,15,16,19] data are not homogeneous. Onstenk et al[13] and Antonarakis et al[19] showed no association among CPFS or OS and AR-V7 status (OS HR 1.6; 95% CI 0.6–4.4; $P=.40$[13] and OS HR 2.5; 95% CI 0.8–8.1; $P=.11$[19]). Sher et al[15,16] on the contrary reported significantly ($P<.05$) lower CPFS and OS in AR-V7+ cases submitted to taxane (mean OS 8.9 months in AR-V7+ and 19.8 months in AR-V7−; HR 3.7; 95% CI 1.9–7.1; $P<.001$).

3.4.1. Critical analysis and level of evidences. Several prospective mono or multi-center studies confirmed a significant association between AR-V7 expression and survival parameters in mCRPC cases submitted to abiraterone or enzalutamide. These studies affirmed that abiraterone or enzalutamide treatments are associated with a significantly lower PSA-PFS, CPFS, and OS if an AR-V7 positive expression is detected (level of evidence 2a). Only 2 studies[5,21] comparatively analyzed abiraterone and enzalutamide treatment, showing no significant differences.

Data on CRPC cases submitted to chemotherapies are less homogeneous (level of evidence 2b) and the association between AR-V7 expression and survival parameters such as PSA-PFS, CPFS, and OS is no significant or less evident. Antonarakis et al[19] comparatively analyzed chemotherapies and enzalutamide or abiraterone showing no differences (OS HR between chemotherapies and abiraterone or enzalutamide: 0.83; 95% CI 0.34–2.0 in AR-V7+ and 1.55; 95% CI 0.49–4.95 in AR-V7−; $P=.46$)

3.5. Critical conclusions

Although there are multiple available therapies for men with mCRPC, there are currently no molecular biomarkers to help guide optimal treatment choices in these patients. The recent literature shows an important interest on the determination of AR-V7 expression in PC cases, as prognostic parameter and as indicator for the medical treatment choice.

The determination of AR-V7 in peripheral blood using CTC mRNA seems to be the preferred method.

The clinical usefulness of AR-V7 in hormone-sensitive PC cases is not demonstrated: data are mainly retrospective or limited in no homogeneous populations. It is not possible to hypothesize a role for AR-V7 expression in hormone-sensitive PC as prognostic marker for the treatment choice.

On the contrary in mCRPC treated with abiraterone or enzalutamide, it is well demonstrated that AR-V7+ patients have inferior clinical outcomes compared with AR-V7 negative cases, with respect to PSA response, PSA-PFS, CPFS, and OS. The

AR-V7 status has the same impact on abiraterone or enzalutamide response and in some experiences, no AR-V7 positive case had an appreciable clinical benefit from enzalutamide or abiraterone. The impact of this biomarker is less relevant in patients selected for chemotherapies and its expression is not associated with a significant resistance to taxane. The suggestion is that taxane therapy is more efficacious than abiraterone or enzalutamide for men with AR-V7 positive CRPC. On the contrary, clinical outcomes did not seem to differ significantly on the basis of the type of therapy used among AR-V7 negative cases.

All these trials showed relevant limitations. For example, those trials focusing on Chemotherapy treatment did not consider whether patients received any and which treatment before or how long after treatment patients were diagnosed with mCRPC. We, therefore, cannot obtain final conclusion on a definitive role of AR-V7 in the prediction of response or in the selection of mCRPC cases for different treatments.

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References

[1] Luo J, Attard G, Balk SP, et al. Role of androgen receptor variants in prostate cancer: report from the 2017 mission androgen receptor variants meeting. Eur Urol 2018;73:715–23.
[2] Takeuchi T, Okuno Y, Hattori-Kato M, et al. Detection of AR-V7 mRNA in whole blood may not predict the effectiveness of novel endocrine drugs for castration resistant prostate cancer. Res Urol 2016; 8:21–5.
[3] Gillessen S, Attard G, Beer TM. Management of patients with advanced prostate cancer: the report of the advanced prostate cancer consensus conference. Eur Urol 2018;73:178–211.
[4] Crumbaker M, Savdie R, Joshua AM. Refining the assessment and implications of AR-V7 in castrate-resistant prostate cancer. Eur Urolo 2018;73:736–7.
[5] Antonarakis ES, Lu C, Wang H. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. N Engl J Med 2014;371:1028–38.
[6] Luo J. Development of AR-V7 as a putative treatment selection marker for metastatic castration resistant prostate cancer. Asian J Androl 2016;18:580–5.
[7] Henzler C, Li Y, Yang R. Truncation and constitutive activation of the androgen receptor by diverse genomic rearrangements in prostate cancer. Nat Commun 2016;7:13668–73.
[8] Del Re M, Biasco E, Crucitta S. The detection of androgen receptor splice variant 7 in plasma-derived exosomal RNA strongly predict resistance to hormonal therapy in metastatic prostate cancer patients. Eur Urol 2017; 71:680–7.
[9] Markowski MC, Silberstein JL, Eshleman JR, et al. Clinical utility of CLIA-grade AR-V7 testing in patients with metastatic castration resistant prostate cancer. JCO Precision Oncol 2017;1:1–9.
[10] Heidenreich A, Bellmunt J, Bolla M, et al. EAU guidelines on prostate cancer. Part 1: screening, diagnosis and treatment of clinically localized disease. Eur Urol 2011;59:61–71.
[11] Seits AK, Thoene S, Bietenbeck A, et al. AR-V7 in peripheral blood of patients with castration resistant prostate cancer: association with treatment-specific outcome under abiraterone and enzalutamide. Eur Urol 2017;72:828–34.
[12] Todenhofer T, Azad A, Stewart C, et al. Ar-V7 transcripts in whole blood RNA of patients with metastatic castration resistant prostate cancer correlate with response to abiraterone acetate. J Urol 2017;197:135–42.
[13] Onstenk W, Sieuwerts AM, Kraan J, et al. Efficacy of cabazitaxel in castration resistant prostate cancer is independent of the presence of AR-V7 in circulating tumor cells. Eur Urol 2015;68:939–45.
[14] Antonarakis ES, Lu C, Luber B, et al. Clinical significance of androgen receptor splice variant-7 mRNA detection in circulating tumor cells of men with metastatic castration resistant prostate cancer treated with first and second line abiraterone and enzalutamide. J Clinical Oncol 2017;35:2149–57.
[15] Scher HI, Lu D, Schreiber NA, et al. Association of AR-V7 on circulating tumor cells as a treatment specific biomarker with outcomes and survival in castration resistant prostate cancer. JAMA 2016;2:1441–9.
[16] Scher HJ, 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.
[17] Bernemann C, Schnoeller TJ, Luedeke M, et al. Expression of AR-V7 in circulating tumor cells does not preclude response to next generation androgen deprivation therapy in patients with castration resistant prostate cancer. Eur Urol 2017;71:1–3.
[18] Chen X, Bernemann C, Tolkach Y, et al. Overexpression of nuclear AR-V7 in primary prostate cancer is an independent negative prognostic marker in men with high risk disease receiving adjuvant therapy. Urol Oncol 2018;36:19–31.
[19] 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.
[20] Li H, Wang Z, Xiao W, et al. androgen receptor splice variant 7 positive prostate cancer: a novel molecula subtype with markedly worse androgen deprivation therapy outcomes in newly diagnosed patients. Modern Pathol 2018;31:198–208.
[21] Qu F, Xie W, Nakabayashi M, et al. Association of AR-V7 and prostate specific antigen RNA levels in blood with efficacies of abiraterone acetate and enzalutamide treatment in men with prostate cancer. Clin Cancer res 2017;23:726–34.