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Platinum Priority – Editorial

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Investigating Genomic Aberrations of the Androgen Receptor: Moving Closer to More Precise Prostate Cancer Care?

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In this issue of *European Urology*, De Laere and colleagues [1] report on a study profiling the androgen receptor (AR) in patients with metastatic castration-resistant prostate cancer (mCRPC), evaluating blood-based assays to analyze serial tumor mRNA and DNA from circulating tumor cells (CTCs) and cell-free DNA (cfDNA). In their study, AR aberrations including point mutations, copy number gains, structural variations, and alternatively spliced forms of AR were frequent among mCRPC patients, particularly after exposure to abiraterone and enzalutamide; these events were detectable from plasma samples. This study builds on published data on AR genomic aberrations and endocrine therapy resistance.

Persistent AR signaling despite androgen deprivation therapy (ADT) is an established feature of mCRPC; further targeting of this pathway results in tumor responses, as shown with the successful development of abiraterone acetate and enzalutamide. Yet, not all patients respond to these drugs, with response duration being limited and resistance invariably emerging. A number of studies have associated primary or secondary resistance to abiraterone and enzalutamide with specific AR aberrations that result in continued, and ligand-independent, AR transcriptional activity (Table 1).

Henzler et al [2] recently found AR structural genomic rearrangements in up to one-third of mCRPC tumor tissue samples, identifying intrapatient and interpatient heterogeneity, with subclonal enrichment for some of these events. It has been reported that these AR structural rearrangements generate AR splice variants; these are constitutively active despite the absence of androgenic steroid ligands through retention of the AR N-terminus (AR-NTD) and associated activation function-1 (AF-1) essential for hormone-independent AR transactivation and loss of the regulatory carboxy-terminal ligand-binding domain (LBD). It has been reported that these AR splice variants are a key mechanism of resistance to androgen deprivation therapy.

Previous studies using cfDNA to detect copy-number changes and hotspot mutations associated the emergence of AR genomic aberrations with resistance to abiraterone and enzalutamide [3,4]. Similarly, detection of AR splice variants in CTCs has been related to poor response to endocrine therapy, but not taxanes, and survival [5–8]. While most of these studies have focused on AR splice variant 7 (AR-V7), which may not be generated by AR structural rearrangements, several studies show that there are many different AR splice variants and some of these result in constitutively active forms that are detectable in CRPC samples.

The use of blood-based assays in this study is clinically important; if AR genomic aberrations arise after the start of endocrine therapy, there is a need for assays that are repeatable and preferably noninvasive. cfDNA may also allow evaluation of intrapatient heterogeneity of clonal evolution. It is also important to recognize that these biomarker studies were largely carried out retrospectively, utilizing different analytical assays in heterogeneous and relatively small patient cohorts (Table 1), so prospective validation trials are now needed, particularly since the presence of these biomarkers with resistance to abiraterone and enzalutamide does not always associate with treatment resistance, perhaps because of intrapatient heterogeneity [8]. Emerging data from preclinical studies also report

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Table 1 – Studies determining androgen receptor aberrations and their impact on clinical outcome

Assay	Aberration	Treatment	Clinical impact
Plasma DNA			
Targeted DNA sequencing [3]	AR CN gain (40%) AR T878A or L702H mutant (5%)	Abiraterone (80 pts)	AR aberration (CN gain and AR mutant) vs AR CN neutral patients PSA 50% RR: OR 4.9; $p = 0.002$ [a] PFS: HR 3.73; $p = 2 \times 10^{-6}$ [b,c] OS: HR 7.33; $p = 1.2 \times 10^{-7}$ [b,c]
CTCs			
RT-PCR [5]	AR-V7 (RNA) positive (19%)	Abiraterone (31 pts)	AR-V7 positive vs AR-V7 negative patients: PSA 50% RR: 0% vs 68%; $p = 0.004$ [a] PSA PFS: 1.3 mo vs NR; HR 16.1; $p < 0.001$ [b,c] Clinical/radiological PFS: 2.3 mo vs NR; HR 16.5; $p < 0.001$ [b,c] OS: 10.6 mo vs NR; HR 12.7; $p = 0.006$ [b,c]
	AR-V7 (RNA) positive (39%)	Enzalutamide (31 pts)	AR-V7 positive vs AR-V7 negative patients: PSA RR: 0% vs 53%; $p = 0.004$ [a] PSA PFS: 1.4 vs 6.0 mo; HR 7.4; $p < 0.001$ [b,c] Clinical/radiological PFS: 2.1 vs 6.1 mo; HR 8.5; $p < 0.001$ [b,c] OS: 5.5 mo vs NR; HR 6.9; $p = 0.002$ [b,c]
RT-PCR [12]	AR-V7 (RNA) positive (46%)	Docetaxel (30 pts) and cabazitaxel (7 pts)	AR-V7 positive vs AR-V7 negative patients: PSA 50% RR: 41% vs 65%; $p = 0.19$ [a] PSA PFS: 4.5 vs 6.2 mo; HR 2.1; $p = 0.06$ [b,c] Clinical/radiological PFS: 5.1 vs 6.9 mo; HR 2.8; $p = 0.02$ [b,c] OS; 9.2 vs 14.7 months; HR 2.5; p=0.11[bc] AR-V7 positive patients demonstrated improved 50% PSA RR (41% vs 0%; $p < 0.001$ [a]) PSA PFS (HR 0.22; $p < 0.001$ [c]), clinical/radiological PFS (HR 0.26; $p = 0.001$ [c]), and OS (HR 0.83; $p = 0.76$ [c]) with taxane treatment compared to AR-targeted therapies (compared to REF; updated analysis). There was no benefit of taxane treatment over AR-targeted therapies in AR-V7 negative patients
IF [6]	AR-V7 (protein) positive (12.5%)	Abiraterone, enzalutamide, and apalutamide (128 pts)	AR-V7 positive vs AR-V7 negative patients: rPFS: 2.3 vs 14.5 mo; HR 2.3; $p < 0.001$ [b,c] Time on therapy: 2.1 vs 6.8 mo; HR 4.2; $p < 0.001$ [b,c] OS: 4.6 mo vs NR; HR 11.45; $p < 0.001$ [b,c]
	AR-V7 (protein) positive (28.6%)	Docetaxel, cabazitaxel, and paclitaxel (63 pts)	AR-V7 positive vs AR-V7 negative patients: rPFS: 5.3 vs 6.6 mo; HR 1.38; $p = 0.46$ [b,c] Time on therapy: 3.0 vs 3.7 mo; HR 1.40; $p = 0.23$ [b,c] OS; 8.9 vs NR; HR 3.74; p=0.001[bc] AR-V7 positive patients had favorable survival on taxane therapy compared to ARSi (HR 0.24; $p = 0.035$ [d]) while AR-V7 negative patients did not
Targeted RNA sequencing [1]	AR-V (RNA) positive (47%)	Abiraterone (15 pts) and enzalutamide (2 pts)	AR-V positive vs AR-V negative patients: PSA 50% RR: 44% vs 12.5%; $p = 0.29$ [a] PFS HR 4.53; $p = 0.0105$ [b,c]
Tissue			
IHC [13]	Nuclear AR-V7 (protein) expression	Various (37 pts)	Nuclear AR-V7 expression levels by tertiles (3rd vs 2nd vs 1st): OS from metastatic biopsy: 7.1 vs 10.7 vs 15.6 mo; HR 2.9; $p = 0.002$ [b,c]

CTCs = circulating tumor cells; IF = immunofluorescence; IHC = immunohistochemistry; AR = androgen receptor; CN = copy number; pts = patients; PSA = prostate-specific antigen; RR = response rate; PFS = progression-free survival; OS = overall survival; OR = odds ratio; HR = hazard ratio; RT-PCR = reverse transcription polymerase chain reaction; AR-V7 = androgen receptor variant 7; AR-V = androgen receptor variant; NR = not reached; ARSi = androgen receptor signaling inhibitor; rPFS = radiological PFS.

[a] Fisher's exact test.

[b] Kaplan-Meier method with log-rank test.

[c] Univariate Cox regression analyses.

[d] Multivariate Cox regression analyses.

alternative adapting mechanisms that can overcome AR blockade, and these also need to be evaluated [9].

The genomic AR aberrations described in this report appear common in CRPC but seem to be infrequent in localized prostate cancers before androgen deprivation. These probably primarily evolve as a result of treatment-induced selective pressures, although AR splice variants may be present in untreated prostate tumors [10]. Whether these events appear de novo or are a result of the selection of subclones that become more prominent after therapy needs further consideration and may be relevant when selecting early treatment for both localized and metastatic disease.

The mechanisms resulting in the emergence of these complex intra-AR rearrangements also merit discussion. Aberrant DNA damage responses, frequently present in mCRPC, and the resulting genomic instability may contribute to the generation of these structural genomic

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