Prostate cancer

AR aberrations and resistance to abiraterone or enzalutamide

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Resistance to abiraterone or enzalutamide after previous hormonal therapy is increasingly likely and cross-resistance often occurs when these two agents are given sequentially. Blood-based analysis of AR mRNA splice variants and AR genomic mutations may aid ourThus, an increased understanding of the mechanisms of resistance to these drugs in order to is required in order to better manage patients with castration-resistant prostate cancer.

Refers to Bernemann, C. *et al*. Expression of AR-V7 in circulating tumour cells does not preclude response to next generation androgen deprivation therapy in patients with castration r esistant prostate cancer. *Eur. Urol*. http://dx.doi.org/10.1016/j.eururo.2016.07.021 (2016)

Abiraterone and enzalutamide are now widely used as standard treatments for castration-resistant prostate cancer (CRPC). Overall, >90% of patients show a decline in serum PSA levels when treatment is initiated as first-line CRPC
therapy, but increasing lines of previous hormonal therapy amplifiesincrease the likelihood of primary resistance[1]. Moreover>20% of men experience a PSA concentration decline with the second agent when abiraterone or enzalutamide are used sequentially. A change in PSA levels is commonly used as an objective end point in phase II clinical trials (especially those testing androgen-receptor (AR)-targeting compounds)[2], but the duration of benefit for abiraterone or en zalutamide is variable even for men who respond to treatment — some men experience an exc eptional long-term response,
continuing treatment for several years, whereas other patients progress clinically within months. Thus, we urgently need to understand the mechanisms of resistance to abiraterone and enzalutamide and develop biomarker approaches that can be used to improve the management of patients with CRPC.

AR splice variants (AR-Vs) and/or genomic *AR* aberrations are associated with resistance to abiraterone or enzalutamide. AR-Vs lacking the ligand-binding domain (LBD) maintain AR-regulated transcription in multiple *in vitro* and *in vivo* enzalutamide and/or abiraterone-resistant models[3]. Detection of the AR-V7 splice

variant in circulating tumour cells (CTCs) from men with CRPC is strongly associated with a reduced rate of PSA decline and decreased progression-free and overall survival with abiraterone or enzalutamide treatment[4,5].

Similarly, detection of *AR* amplification or specific point mutations in circulating cell-free DNA (ccfDNA) is also associated with resistance to abiraterone or enzalutamide[6-9]. Liquid biopsies th at define AR-Vs and/or *AR* genomic status at the same time (for example integrated *AR* analysis at the mRNA and DNA level) could, therefore, identify patients li kely to derive limited benefit from potent AR-LBD targeting with drugs such as abiraterone and e nzalutamide and pre-emptively offer alternative treatments.

The success of this approach is dependent on the efficacy and selectivity of an agent for targeting the aberrant AR population. Preliminary data suggest that positive AR-V7 status is not necessarily associated with resistance to taxanes [10]. Taxane chemotherapy might not be select ively effective in AR-aberrant cancers but could offer an opportunity for improving the treatment of this population of men. New agents designed to target the AR lacking the LBD are in development[11,12] and could offer an opportunity to improve outcomes for these patients.

Whether the presence of aberrant AR is uniformly associated with treatment resistance to AR-directed therapy is not known. A study by Bernemann *et al.*[13] reported that some patients (4/21) with putatively AR-V7-positive CTCs[13] achieved 50% PSA level reductions when treated with abiraterone or enzalutamide, although these biochemical responses were relatively short-lived. Preliminary data from other studies support these findings with occasional PSA declines reported in patients with AR-V7-positive prostate cancer [1 4]. Most data support the notion that AR-V7, similar to *AR* genomic aberrations[15 10], could be late events involved in treatment resistance that are often subclonal. For example both AR-V7-negative and AR-V7-positive CTCs are sometimes detected in the same patient[16], which could lead to clinical scenarios in which responses are variable or PSA levels decline briefly; however overall, the duration of benefit for patients with CTCs expressing AR-V7 is short . Data from patients with

AR gene aberrations detected in ccfDNA have shown similar results, with some patients exhibiting a decline in PSA concentrations that generally proves to be more transient than patients with normal *AR* ~~de~~tected in ccfDNA [6]. The association of AR-V7 expression with resistance could be dose-dependent or contingent upon coexisting factors and further stratification could improve prediction. However, this multi-hit scenario would still suggest that AR-V7-expressing cancers are more likely to develop resistance sooner than those that do not. Thus, we agree with Bernemann and colleagues[13] that the presence of AR-V7 in CTCs does not necessarily preclude PSA responses to abiraterone or enzalutamide, but the durability of such responses must also be evaluated before concluding that these patients derive meaningful clinical benefit from these novel hormonal agents. In this context, swimmers plots could be helpful to show the duration of treatment effect in small cohorts and enable appreciation of short benefit in patients despite a decline in PSA concentrations. In the paper by Bernemann and co-workers [13], the longest PSA response to novel AR-targeting therapy in patients with AR-V7-positive CTCs was 6.2 months, which is considerably shorter than the median PSA progression-free survival expected with these agents in this setting. Finally, interpretation of the results depends on robust and accurate detection of the biomarker in question by using analytically validated biomarker assays before applying these to a clinical setting. Whether the assay performed by Bernemann *et al.*[13] was carefully validated and standardized for this clinical study is unclear, and the results should, therefore, be interpreted with some degree of caution.

In conclusion, treatment selection based on AR-V7 status remains an experimental approach that should not be conducted outside the setting of a clinical trial at the present time. The clinical utility of detecting AR-V7 (in CTCs, cell-free nucleic acids or tumour tissue) will rely on robust analytical validation of each biomarker assay and will depend on alternative treatment options and clinical trials to address this challenge in a prospective fashion. Before the availability of such conclusive results, patients with AR-aberrant disease should certainly be considered for abiraterone or enzalutamide treatment in the appropriate clinical setting.

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Competing interests

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