

## **Androgen receptor aberrations and abiraterone/enzalutamide-resistant prostate cancer**

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Abiraterone and enzalutamide are now widely used as standard treatments for castration-resistant prostate cancer (CRPC). Over 90% of patients show a decline in PSA when treatment is initiated as first-line CRPC therapy but primary resistance is more common after an increasing number of lines of prior hormone therapy<sup>1</sup>. Moreover, fewer than 20% of men have a PSA decline with the second agent when abiraterone or enzalutamide are used sequentially. Although a change in PSA is commonly used as an objective end-point in Phase II clinical trials (especially those testing androgen receptor-targeting compounds)<sup>2</sup>, the duration of benefit to abiraterone or enzalutamide is variable even in PSA responders with long-term exceptional responders continuing treatment for several years whilst other patients progress clinically within months. There is therefore an urgent need to understand resistance to abiraterone and enzalutamide and develop biomarker approaches that can be used to improve the management of CRPC patients.

Androgen receptor splice variants and/or genomic *AR* aberrations have been shown to associate with resistance to abiraterone or enzalutamide. *AR* variants lacking the ligand-binding domain (LBD) maintain *AR*-regulated transcription in multiple in vitro and in vivo enzalutamide/abiraterone-resistant models<sup>3</sup>. Detection of the *AR*-V7 splice variant in circulating tumor cells (CTC) from CRPC patients strongly associates with a lower rate of PSA decline and a shorter progression-free and overall survival with abiraterone or enzalutamide<sup>4,5</sup>. Similarly, detection of *AR* gene amplification or specific point mutations in circulating cell-free DNA (ccfDNA) also associates with resistance to abiraterone or enzalutamide<sup>6-9</sup>. Liquid biopsies that define *AR* splice variant and/or *AR* genomic status at the same time (i.e. integrated *AR* analysis at the mRNA and DNA level) could therefore identify patients likely to derive limited benefit from potent *AR*-LBD-targeting with drugs like abiraterone or enzalutamide and pre-emptively offer alternative treatment.

The success of this approach is dependent on the efficacy and selectivity of an agent for targeting the aberrant *AR* population. Preliminary data suggest the absence of an association with resistance to taxanes in *AR*-V7 positive cancers<sup>10</sup>. Taxane chemotherapy may not be selectively effective in *AR* aberrant cancers but could offer an opportunity for improving the treatment of this population. Newer agents designed to target the *AR* lacking the LBD are in development<sup>11,12</sup> and could offer an opportunity to improve the outcomes for these patients.

However, is the presence of aberrant AR uniformly associated with treatment resistance to AR-directed therapy? A study by Bernemann *et al.* in a recent issue of *European Urology* reported that some patients (4/21) with putatively AR-V7-positive CTC<sup>13</sup> achieved 50% PSA reductions to abiraterone/enzalutamide although these biochemical responses were relatively short-lived. Is this result surprising or biologically plausible? Preliminary data from other studies also support these findings with occasional PSA declines reported in AR-V7-positive patients<sup>14</sup>. Most data support the notion that AR-V7, similar to AR genomic aberrations<sup>15 10</sup> may be late events involved in treatment resistance that are often sub-clonal; for example both AR-V7–negative and -positive CTCs are sometimes detected in the same patient<sup>16</sup>. This could lead to clinical scenarios with variable responses or brief PSA declines but overall a shorter duration of benefit for patients with CTCs expressing AR-V7. This has also been found to be the case for patients with AR gene aberrations detected in ccfDNA, with some patients exhibiting a decline in PSA that generally proves to be more transient than ccfDNA AR gene normal patients<sup>6</sup>. It is also possible that the association of AR-V7 expression with resistance is dose-dependent or contingent upon co-existing factors and further stratification could provide more accurate prediction. However, this multi-hit scenario would still suggest that AR-V7-expressing cancers are more likely to develop resistance sooner. Therefore, while we agree with Bernemann *et al.* that the presence of AR-V7 in CTCs does not necessarily preclude PSA responses to abiraterone or enzalutamide, 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 on treatment in small cohorts and allow appreciation of shorter benefit in patients despite a decline in PSA. In the Bernemann *et al.* paper, the longest PSA response to novel AR-targeting therapy in an AR-V7–positive patient was 6.2 months, which is significantly 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 previously analytically validated biomarker assays before applying these to a clinical setting. It is unclear if the Bernemann *et al.* assay was carefully validated and locked down prior to the conduct of this clinical study, and the results should therefore be interpreted with some degree of caution.

In conclusion, treatment change or 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 tumor tissues) will rely

on robust analytical validation of each biomarker assay and will depend on alternative treatment options and clinical trials to address this question in a prospective fashion. Prior to the publication of such conclusive results, AR-aberrant patients should certainly be considered for abiraterone or enzalutamide treatment in the appropriate clinical setting.

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