Validation of AR-V7 as a Treatment-Specific Biomarker at Decision Points in Management of Castration-Resistant Prostate Cancer

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Background

Androgen receptor signaling directed therapies (AR-Tx), including Abiraterone Acetate + Prednisone (A) and Enzalutamide (E), prolong survival in patients with mCRPC and FDA approved. The presence of the splice variant AR-V7 mRNA in EPAM selected CTCs has been prospectively linked to resistance to A & E but not to taxane chemotherapy (T). AR-V7 may provide clinical utility in therapy selection between A & E or T. A key limitation to the predictive value of an AR-V7 mRNA assay in CTCs is the analytical validation of the measurement of low frequency and unstable mRNA in CTCs, and to be able to report diverse pathological workflows amenable to community practices. Separately, EpCAM based CTC isolation and capture methods will not detect EpCAM- cells, potentially leading to under-sampling of the AR-V7 biomarker. We developed an AR-V7 immunoassay. The specificity of AI therapy results in clinical outcomes following treatment with the most approved, rapid assays for management of mCRPC AR-Tx and taxanes. The goal is the development of predictive biomarkers for use at the point a treatment decision is needed that will enable broad adoption from clinical practice.

Methods

181 patients were selected from AR-Tx and taxane therapy naïve patients. AR-V7 status was assessed on patient blood samples by three methods: 1) EPAM, 2) CTC isolation and capture methods, and 3) AR-V7 test. AR-V7 status was considered resistant (R) or sensitive (S). Pretherapy AR-V7 status was compared to posttherapy AR-V7 status.

Results

The prevalence of AR-V7 varied between patient groups: AR-V7(+): 42% (56 samples), AR-V7(-): 58% (125 samples). Patients were separated into two groups AR-V7(+): 65 samples, AR-V7(-): 116 samples. All patients were followed for 6 months or until death.

Conclusion

AR-V7 is an independent predictor of overall survival and corticosteroids were associated with worse outcomes. AR-V7(+) patients who developed corticosteroids had a significantly shorter overall survival than AR-V7(-) patients (HR=11.45, 95% CI: 5.67–23.14, p < 0.0001). AR-V7 status was not significantly different by AR-Tx or taxane status. When compared to patients classified as AR-V7(-), AR-V7(+) patients had shorter overall survival when exposed to corticosteroids (HR=3.74, 95% CI: 1.50–9.21, p < 0.005).

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Conclusions

- AR-V7 expression in CTCs of mCRPC patients assessed through the Epic Sciences platform is comparable with diagnostic workflows (median 34 hours from draw to processing).
- AR-V7 prevalence increases with increased exposure to systemic therapy: AR-Tx (p < 0.0001) but not with AR-E. This represents a minority population of total CTCs suggestive of disease heterogeneity.
- AR-V7 expression on EpCAM CTCs is 100% specific (100% PVV) to de novo PSA resistance, and predicts shorter time on drug (HR=6.15, p<0.001), shorter PFS (HR=2.86, p<0.001), and shorter OS (HR=11.4, p<0.001) of patients receiving AR-Tx.
- AR-V7 expression is not associated with PSA resistance, time on drug, or on-taxane in taxane treated patients.
- The detection of nuclear AR-V7 positive CTCs in men with progressive mCRPC supports the selection of taxane based therapy over AR directed therapies. Doing so was associated with a 76% reduction in the risk of death (HR=0.24, p<0.001) relative to the use of AR-directed therapy. AR-V7+ patients had longer overall survival with the use of AR-E/C and taxane therapy AR-V7(-), relative to those without (median 6.4 months, p<0.001).

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