

Impact of AR-V7 protein localization in the prediction of therapeutic benefit of Taxanes over Androgen Receptor Signaling inhibitors (ARSi) in metastatic Castration Resistant Prostate Cancer (mCRPC)

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Background: AR-V7 is a truncated form of the AR lacking the ligand binding domain that activates AR signaling in the absence of androgens. The presence of AR-V7 mRNA in CTCs predicts a poor outcome on the ARSi, abiraterone and enzalutamide. Localization of AR-V7 in the nucleus of CTCs also predicts poor ARSi outcomes, and a treatment-specific interaction that predicted a reduced risk of death if Taxanes vs. ARSi (HR = 0.242, p = 0.0350) are prescribed. Overall, the incidence of nuclear AR-V7 protein was lower than that of AR-V7 mRNA, but more predictive of ARSi outcomes. In a post-hoc analysis of outcomes of samples evaluated with AR-V7 CTC protein we asked if the presence of cytoplasmic AR-V7 protein could explain the difference in prognostic ability of the two tests, and separately, explored the association between non-nuclear AR-V7 and benefit from taxanes over ARSi.

Methods: 191 blood samples (n = 128 pre-ARSi, n = 63 pre-Taxane) from 161 patients were processed utilizing the Epic Sciences CTC nuclear AR-V7 protein test. Patients were followed up to 29.5 months (range 1.3 to 29.5). Samples were rescored by readers, blinded to outcome to determine the frequency of and outcome with cytoplasmic AR-V7.

Results: Inclusion of non-nuclear localized AR-V7 protein as positive scoring criteria increased the incidence of detection in all lines of therapy, an equivalent increase in false positives (PSA responders), and loss of the significance of the treatment-specific survival interaction in multivariate model.

AR-V7 Localization	Detection Rate by Line of Therapy (1 st , 2 nd , 3 rd +)	HR of OS on ARSi	Therapy Interaction (Taxanes vs. ARSi)
Nuclear (alone)	3%, 18%, 31%	10.4, p < 0.0001	0.242, p = 0.0350
Cytoplasmic (alone)	13%, 8%, 12%	1.11, p = 0.844	1.21, p = 0.838
Any (Nuc & Cyto)	16%, 26%, 43%	4.3, p < 0.0001	1.04, p = 0.943

Conclusions: Including cytoplasmic AR-V7 in the "positive" test definition reduces the prognostic power of the assay and negates the treatment predictive value of AR-V7. Not all AR-V7 signal is equivalent. It remains to be seen if non-nuclear localized AR-V7 protein samples would test positive via mRNA methods.

COI: RP, DL, JL, LD & RD are employees of Epic Sciences

Funding Support: MSKCC SPORE in Prostate Cancer (P50 CA92629), the Department of Defense Prostate Cancer Research Program (PC051382), NIH/NCI Cancer Center Support Grant P30 CA0098748, The Prostate Cancer Foundation, and the David H. Koch Fund for Prostate Cancer Research.