AR-V7 Status and CTC Heterogeneity Improve the Prediction of Drug Sensitivity and Patient Outcomes for Taxanes and Approved AR Targeted Therapies

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Background

A critical unmet need in the management of mCRPC is how to use currently approved agents to maximize survival for the individual patient. Outcomes to AR signaling inhibitors such as, abiraterone acetate and enzalutamide (AR-Tx), and taxane based chemotherapy, the two most commonly used drug classes, vary with in vivo efficacy and sequence of administration, but cross-sensitivity and resistance are not predictable at the individual patient level when a treatment decision is required.

We recently identified a statistically significant therapy interaction between nuclear AR-V7 protein expression in CTCs and improved OS with Taxanes over AR Tx (HR=0.256, p=0.035) supporting taxane use for AR-V7+ patients. Similarly, high AR heterogeneity in mCRPC patients also demonstrated a therapy interaction supporting Taxanes over AR Tx (HR=0.302, p=0.022). We studied both markers in a single cohort and related the two biomarkers to clinical outcomes.

Methods for CTC Detection; Phenotypic, Genomic Characterization, and Heterogeneity Score

1) Heterogeneous CTC samples from 31 unique patients were analyzed with the Epic Sciences platform. Analysis included digital pathways of 23 discrete genotypic, phenotypic, and biomarker analysis workflows:
   a) Single Cell Features: Core sample single cell data stored and curated in a 23 pathways of individual data analysis workflows. Multiple multi-parametric digital pathology algorithms defined by human pathologist review were independently and systematically applied to each data set.
   b) Phenotypic Features: Core sample single cell data stored and curated in a 23 pathways of individual data analysis workflows. Multiple multi-parametric digital pathology algorithms defined by human pathologist review were independently and systematically applied to each data set.
   c) Genomic Features: Core sample single cell data stored and curated in a 23 pathways of individual data analysis workflows. Multiple multi-parametric digital pathology algorithms defined by human pathologist review were independently and systematically applied to each data set.
   d) Heterogeneity Score: Core sample single cell data stored and curated in a 23 pathways of individual data analysis workflows. Multiple multi-parametric digital pathology algorithms defined by human pathologist review were independently and systematically applied to each data set.

2) Heterogeneity Score

Patients with AR-V7+ and High Heterogeneity have improved OS times with Taxane combination, AR-V7+ only, and AR-V7+/Het+.

Conclusions

• Nuclear AR-V7 protein expression and high phenotypic heterogeneity, when analyzed separately and in combination, predict poor outcomes on AR Tx or in combination.
• AR-V7 nuclear positivity is strongly associated with high phenotypic heterogeneity (OR= 6.3, p<0.0001).
• Patients with both nuclear AR-V7 and high heterogeneity have the worst outcome on AR Tx (HR=22.7, p<0.0001) and the strongest prediction of benefit from taxane therapy vs. ARs by hazards of death reduction (HR=6.20, p=0.01).
• Single CTC sequencing highlights high genomic complexity with multiple drivers of disease progression in AR-V7+ and overall survival.

Support: NIH/NCI (P50CA92629), MSKCC SPORE in Prostate Cancer (P50 CA92629), Department of Defense Prostate Cancer Research Program (PC051382), NIH/NCI SPORE in Prostate Cancer (P50CA92629), NCI/DOE/DOE Cancer Center Support Grant (P30CA036700), The Prostate Cancer Foundation, and the David H. Koch Fund for Prostate Cancer Research.