Role of AR-V7 and AR-FL in resistance to hormonal therapy in mCRPC: Independent actors or reciprocal drivers? A translational study by Meet-Uro group

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Background: The androgen receptor splice variant 7 (AR-V7) is strongly associated with resistance to hormonal therapy (HT) in castration-resistant prostate cancer (CRPC), although it is not implemented in clinical practice as a biomarker. The AR-full length (AR-FL) is also overexpressed in CRPC but its role has yet to be clarified. The aim of the present work was to investigate the role of AR-V7 and AR-FL as predictors of resistance to HT in plasma-derived exosomal RNA.

Methods: 6 ml of blood were collected in EDTA tubes before the start of abiraterone/ enzalutamide; blood was centrifuged and plasma stored at -80°C until analysis. Exosomes isolation and RNA extraction were performed using the exoNeasy kit (Qiagen) as per manufacturer instructions. The analysis of AR-FL and AR-V7 were performed by digital droplet PCR using the One-Step RT-ddPCR kit (BioRad). The absolute target concentration as copies/ml in samples was calculated by ddPCR QuantaSoft and statistical analyses were performed by SPSS v.24.

Results: 52 patients (pts) were enrolled; AR-FL was detected in all pts (median: 700 copies/ml), while 15 subjects (28.8%) were AR-V7+ (median: 310 copies/ml) at baseline. The amount of AR-FL was significantly higher in pts AR-V7+ vs AR-V7- (6700 vs 490 copies/ml, p < 0.0001). Median PFS and OS were longer in AR-V7- vs AR-V7+ pts (median PFS 23 vs 4 mo, p < 0.0001; median OS 38 vs 9 mo, p < 0.0001). A ROC curve was calculated for AR-FL in the overall population and 950 copies/ml was identified as cut-off value. Pts were then stratified across this value and it was found that PFS was 22 mo in pts with <950 AR-FL copies/ml vs 4 mo in pts with >950 copies/ml (p = 0.0003). In 12/15 AR-V7+ pts the AR-FL expression was >950 copies/ml while in 3/15 AR-V7+ pts, AR-FL expression was <950 copies/ml; however, their PFS reflected the AR-V7 better than AR-FL status, being, respectively 6, 10, 4 mo. No other clinical variables were correlated with worse PFS at the univariate analysis (i.e. Gleason score ≤7 vs >7, age).

Conclusions: This study demonstrates that resistance to HT may be predicted by AR-V7, making it a clinically relevant biomarker. AR-FL over-expression may contribute to hormone resistance although AR-V7 plays a primary role.

Legal entity responsible for the study: Romano Danesi.

Funding: University of Pisa.

Disclosure: All authors have declared no conflicts of interest.