AR-V7AND AR-FL EXPRESSION IS ASSOCIATED WITH CLINICAL OUTCOME: A TRANSLATIONAL STUDY IN PATIENTS WITH CASTRATE RESISTANT PROSTATE CANCER

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Introduction: The androgen receptor (AR) is the major driver of prostate cancer growth and progression, and dysregulation of the pathway (i.e. amplification, point mutations and splice variants of the AR) may lead to a persistent AR signal transduction. Abiraterone and enzalutamide have become the standard treatment of castration resistance prostate cancer (CRPC). Unfortunately, not all patients respond to hormonal therapy, and this represents a clear clinical need for the identification of predictive biomarkers of poor response to hormonal therapy. In the last years, evidence accumulated suggesting that AR splice variant 7(AR-V7) may be a biomarker of resistance to hormonal therapy and studies reporting its detection on tumour tissue, circulating tumour cells, extracellular vesicles and peripheral blood have been published. Recently, the AR-full length (AR-FL) has also been suggested as a predictive biomarker of response, since the overexpression of the AR-FL was shown to convert prostate cancer growth from a castration-sensitive to a castration-resistant phenotype. The aim of this study was to investigate if the full-length androgen receptor (AR-FL) is associated with resistance to AR-directed therapy independently and/or combined AR-V7.

Patients and methods: Plasma samples were prospectively collected from 73patients with CRPC before first or second-line AR-directed therapy. v.1.1. RNA from plasma-derived exosomes was extracted by the ExoRNeasy kit (Qiagen) and analysed for the expression of AR-FL and AR-V7by digital droplet PCR (BioRad).

Results: AR-FL was detected in all patients while 22% were AR-V7+ at baseline. AR-FL expression was significantly higher in AR-V7+ vs AR-V7- patients ($p<0.0001$). Stratifying patients by tertiles for AR-FL expression, PFS was 22vs 18vs 4months for lower vs intermediate vs higher tertile, respectively ($p=0.0003$). Median PFS and OS were significantly longer in AR-V7- vs AR-V7+ patients (20 vs 4months, $p<0.0001$; not reached vs 9months, $p<0.0001$, respectively).

Discussion and conclusion: Resistance to AR-directed therapy is associated with the presence of AR-V7; however, AR-FL expression may help better refine response and survival of patients to AR directed therapy. Both biomarkers, if validated in prospective trials, may be used to select the best treatment strategy.