# 4 Predicting abiraterone acetate treatment resistance from blood-circulating androgen receptor variants in castration-resistant prostate cancer

European Urology Supplements 2019;18(3):e2429

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**Introduction & Objectives:** Despite the introduction of new pharmacological therapies into clinical practice (e.g. abiraterone acetate, AA), prostate cancer (PCa) remains the second leading cause of cancer-related death among men in developed countries. The majority of mortality is attributed to castration-resistant PCa (CRPC), where around 30% of patients have primary resistance to new hormonal compounds. It has been shown that aberrantly expressed full length androgen receptor (AR-FL) and constitutively active androgen receptor splice variants (AR-Vs) are strongly related to development of AR-directed treatment resistance. Due to the lack of wide spectrum AR transcripts analyses in CRPC, we aimed to evaluate a broader range of blood-circulating androgen receptor transcripts as biomarkers for detection of primary resistance to AA treatment and prediction of progression-free (PFS) and overall survival (OS) in CRPC patients.

**Materials & Methods:** AR-FL, -V1, -V3, and -V7 expression was retrospectively evaluated in 112 PCa specimens (100 cancerous and 12 non-cancerous). Custom made TaqMan assays were designed for further AR transcripts detection in whole blood with quantitative reverse transcription PCR. After technical validation ant pilot study, in the main study the level of AR transcripts was prospectively analyzed in 134 blood samples (14 age-matched controls and 120 serial samples from 66 CRPC patients before (AA-0) and during AA therapy). Continuous and dichotomous (high vs low) levels of the transcripts were rated in various statistical analyses.

**Results:** In tissue study, AR-V7 was significantly overexpressed in cases that subsequently developed biochemical progression (BCR, P=0.010), and BCR-free survival was shorter for those who had higher levels of AR-V7 (P=0.050). Likewise in blood analysis, short (PFS<3 mo) and medium (PFS 3-8 mo) response to AA treatment group had the highest level of AR transcripts in AA-0 samples comparing to extended (PFS>8 mo) response group (AR-V1: P=0.004 and P=0.027, respectively). AR-V1 was detected in 16%, AR-V3 – in 58%, and AR-V7 – in 72% of blood samples. At least one AR-V was found in 82%, while high level of at least one AR-V was observable in 40% of samples. In multivariate analyses, AR-V1 was independent predictor for PFS (continuous P=0.008, dichotomous P=0.040), and together with AR-FL predicted OS (model's P=0.050).

**Conclusions:** Analysis of AR transcripts by whole blood-based assays might be more technically eligible and acceptable in clinical settings and can be used to select patients for AA treatment.