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## Letter to the Editor

**Reply to Ugo De Giorgi, Vincenza Conteduca, and Emanuela Scarpi's Letter to the Editor re: Marzia Del Re, Elisa Biasco, Stefania Crucitta, et al. The Detection of Androgen Receptor Splice Variant 7 in Plasma-derived Exosomal RNA Strongly Predicts Resistance to Hormonal Therapy in Metastatic Prostate Cancer Patients. Eur Urol 2017;71:680–7**

We appreciate the discussion of our recent article on the detection of AR-V7 in plasma and its association with resistance to hormonal therapy in metastatic prostate cancer [1]. The authors commented on some of the data presented in our recent study and communicated their perspectives on the clinical utility of androgen receptor (AR) copy number changes and AR mutations (2105T > A [p.L702H] and 2632A > G [p.T878A]) in castration-resistant prostate cancer (CRPC) [2]. The AR p.T878A mutation occurs in the ligand-binding domain (exon 8) of the AR and alters the steroid binding properties of the receptor [3]. The mutated receptor also experiences activation by progestins, and in the setting of the double mutant also harboring p.L702H, another variant occurring in the ligand-binding domain (exon 4), it binds strongly to enzalutamide in an agonistic manner, which may offer one explanation for resistance to antiandrogen therapies.

AR mutations are the result of clonal selection, depending on the selective pressure of treatment. The appearance of the glucocorticoid-sensitive AR p.L702H and p.T878A mutations in patients given abiraterone provides evidence that these mutations are typical of the adaptive response to antihormonal treatment and confer resistance to this therapy [4]. Moreover, the occurrence of p.L702H and p.T878A mutations in post-docetaxel but not in chemotherapy-naïve abiraterone-treated patients [2] is quite surprising and can probably not be explained by the exposure to cytotoxic drugs, as these are related to the selective pressure by hormonal agents rather than chemotherapeutics.

Therefore, we concur with the necessity for sound methodology and a strong biological and pharmacological rationale for selecting candidate AR variants to be used in investigations of the mechanisms of drug resistance in patients with CRPC. In this context, a direct comparison of exosomes, circulating tumor DNA, and circulating tumor cells (CTCs) in larger studies with homogeneous patient populations could provide the evidence needed to consider these tools as a potential source of a validated circulating biomarker for treatment monitoring.

Although we acknowledge the limitations associated with the lack of direct comparison to CTCs, our study uses the best available evidence concerning resistance to antiandrogen treatment in prostate cancer patients and a standard approach for survival modeling [1]. As suggested by the current scientific literature, AR-V7 determination should be included in the decision-making process with additional efficacy data to make recommendations about the sequencing of therapy for CRPC.

Overall, a substantial amount of scientific information supports the poor prognosis of AR-V7$^+$ patients and the importance of developing novel agents to treat AR-V7$^+$ CRPC, including hormonal agents and immune checkpoint inhibitors [5,6]. From that perspective, we believe that the authors will agree with us on the utility of AR-V7 testing in biomarker-driven trials and in the development of novel agents with activity in this setting.

Finally, we would like to make it clear that our study did not compare plasma-derived exosomes and CTCs, and it focused on the development of alternative methods for AR-V7 detection and the demonstration of any association with clinical variables; validation of the role of AR-V7 as a potential target for treatment is an obvious consequence.

***Conflicts of interest:*** The authors have nothing to disclose.

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