High Sonic Hedgehog (HH) signalling activity, low androgen receptor activity and clonal evolution are associated with resistance to androgen receptor axis inhibitors in patients with metastatic prostate cancer

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Poster n° 1380P

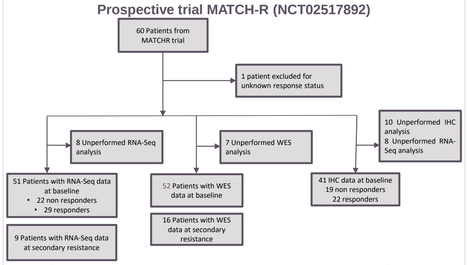
BACKGROUND

The androgen receptor axis inhibitors (ARi) (e.g, enzalutamide, abiraterone acetate) are administered in daily practice for men with metastatic castration-resistant prostate cancer (mCRPC). However, not all patients respond, and mechanisms of both primary and acquired resistance remain largely unknown. The potential mechanisms of reactivated AR may be associated with AR axis (mutation, amplification, overexpression, splice variants), "cross talk" between glucocorticoid receptor and AR, steroidogenesis upregulation, epigenetic alterations, activation of alternative oncogenic signaling, and lineage modification.

OBJECTIVES

The objectives were to identify genomic alterations and alternative oncogenic signaling associated with resistance to ARi as well as to describe clonal evolution.

PATIENTS & METHODS



- **Primary resistance** was determined at 4 months of treatment using composite criteria for progression: serum prostate specific antigen measurements, bone scan, CT imaging and symptom assessments.
- **Acquired resistance** was defined by occurrence of progressive disease after initial response or stable disease.
- Associations of genomic and transcriptomic alterations with primary and or secondary resistance were determined using Wilcoxon and Fisher's exact tests.
- **AR/NEPC Score:** Pearson correlation score between the sample and the reference sample on the expression of each gene of the signature (70 NEPC and 30 AR signature genes).
- **Functional signal transduction pathway activity** (ER, AR, MAPK, HH, NOTCH, TGFβ, PI3K, and Wnt) was determined from RNA-Seq data by OncoSIGNal pathway activity profiling (InnoSIGN, The Netherlands).

RESULTS – PRIMARY RESISTANCE

- At 4 months, 22/55 patients in the cohort had disease progression (primary resistance).
- No genomic alterations from WES analysis were significantly associated with primary resistance (q-value <0.01).

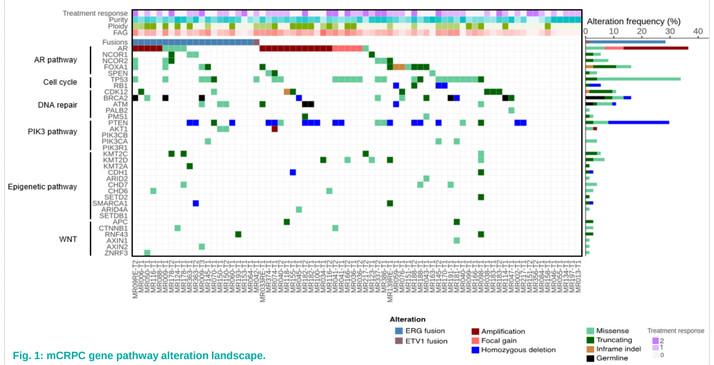


Fig. 1: mCRPC gene pathway alteration landscape.

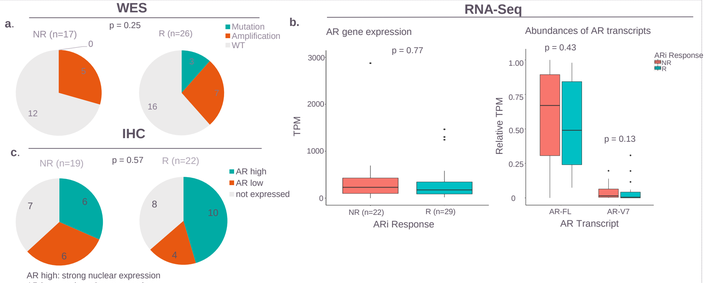


Fig. 2: AR alterations in mCRPC. (a) no statistically significant differences in genomic alterations between the two groups of responders and non-responders. (b) AR gene expression, and its transcripts AR-V7 (AR splice variant) and AR-FL (Full-Length) are not significantly different between responders and non-responders (Wilcoxon test). (c) Similarly, IHC does not show different expression of AR between the two groups. (chi-squared test). (IHC: Immunohistochemistry ; TPM: Transcripts Per Million)

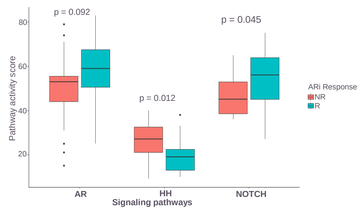


Fig. 3: mRNA-based OncoSIGNal pathway activity profiling. AR, HH, and NOTCH activities in the responder and non responder groups. Negative correlation between AR and HH activities (r= -0.3649, p= 0.009))

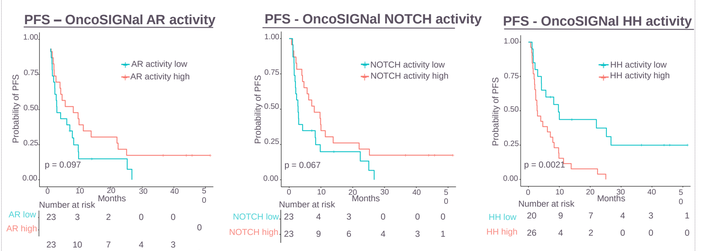


Fig.4: Survival curves with Kaplan Meier analysis for Progression Free Survival (PFS): AR, NOTCH and HH activities

RESULTS – SECONDARY RESISTANCE

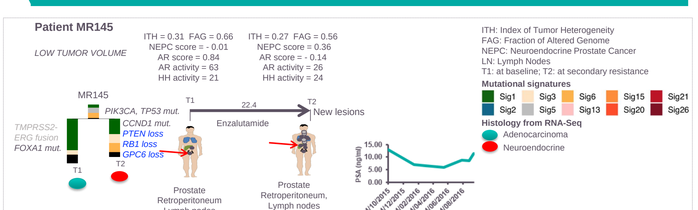


Fig. 5: Examples of clonal evolution model at secondary resistance. Within the 14 molecular histories, 12 show an acquisition of new driver alterations compared to the T1 tumor. Among these acquired alterations, we find an activation of the AR pathway in 5 patients (mutation or amplification of AR, inactivation of NCOR1 and/or NCOR2). It should be noted that BRCA2 was reactivated by 2 independent mutations in patient MR009 who had been treated with a PARP inhibitor, Olaparib.

CONCLUSIONS-PERSPECTIVES

- Although mCRPC is a highly heterogeneous disease, driven by multiple known cancer driver genes, including AR-V7 variants, no predictive values could be determined for AR directed therapy response in mCRPC.
- Clonal evolution analysis along with RNA-Seq data indicate the role of genomic instability and lineage switching in driving acquired resistance.
- OncoSIGNal analysis revealed that low AR and high HH signal transduction pathway activity predict poor clinical response.

Next steps

- Functional validation of HH inhibitors in vivo on mCRPC patient-derived xenograft (PDX) mice is ongoing.
- Further investigate value of signal transduction pathway activity profiling (AR/ HH) for identification of mCRPC patients that will not respond to AR directed therapy and may benefit from (additional) HH inhibitors.

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ACKNOWLEDGEMENTS

We thank the patients for participating to the study.
Conflicts of interests are availaible on ESMO website.

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