Impact of Androgen Receptor Mutations on Immune Infiltration in Castration Resistant Prostate Cancer

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Poster/Abstract # 140

INTRODUCTION

- Castration-resistant prostate cancer (CRPC) frequently harbors mutations in the androgen receptor (AR).
- Understanding the influence of these mutations on the tumor microenvironment is crucial for developing targeted treatment strategies.
- For this study, we leveraged the Tempus Database, which encompasses structured de-identified clinical, imaging, and molecular data, including tumor-normal matched DNA and RNA sequencing.
- Within a cohort of patients with CRPC, we investigated their immune infiltration profile and AR mutational status.

METHODS

- 1556 de-identified patient records of patients with CRPC were analyzed, focusing on AR mutations and amplifications detected from DNA and ARv7 splicing from RNA.
- Immune infiltration was assessed by estimated quantification of immune cell types based on bulk RNA expression using quanTIseq.
- Expression levels of immunotherapy targets (PD-1, PD-L1, CTLA-4),chemokine and cytokine signaling molecules and gene signatures (CYT and GEP) were also evaluated.
- A regression model was developed to study the relationship between AR mutations and immune infiltration, controlling for tumor mutational burden (TMB), tumor purity and sample collection site.

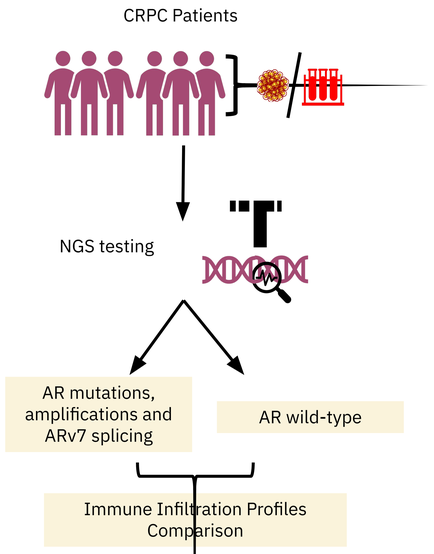

Figure 1. Study flowchart depicting the inclusion of data in this study

SUMMARY

- CRPC patients with AR mutations showed significantly decreased immune infiltration compared to wild-type (WT) counterparts.
- Reduced levels of PD-1, PD-L1, CTLA-4, and chemokine signaling were observed in patients with AR mutations.

RESULTS

Figure 1. Distribution of AR status in the CRPC cohort of the Tempus Database

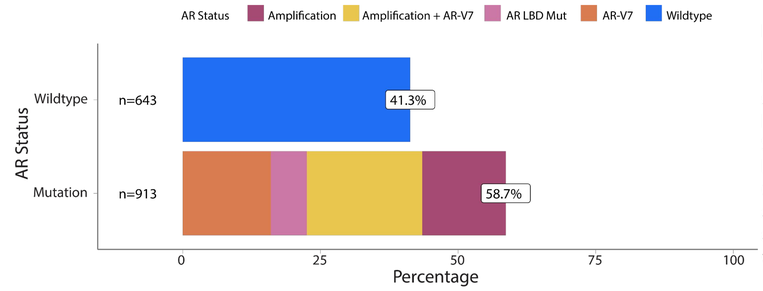

Figure 1. Barplot of patient counts grouped by AR status. The AR status was determined by the presence of AR SNV mutations in the ligand binding domain (AR LBD Mut), AR amplification, ARv7 altered splicing or AR wild type.

Figure 2. Total immune infiltration decreased in AR mutated subgroups

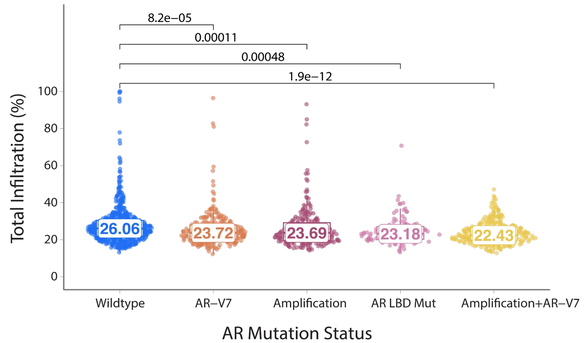

Figure 2. Boxplot and Scatter plot of total immune infiltration across CRPC subgroups. The x-axis represented the subgroups (wild-type, ARv7, AR amplification, AR SNV mutations in the ligand binding domain (AR LBD Mut),and ARv7 altered splicing). The y-axis represents total immune infiltration percentages. Boxplots display median values, with scatter plots indicating individual sample distributions.

Figure 3. Downregulation of immunotherapy targets, chemokine, and cytokine gene expression across

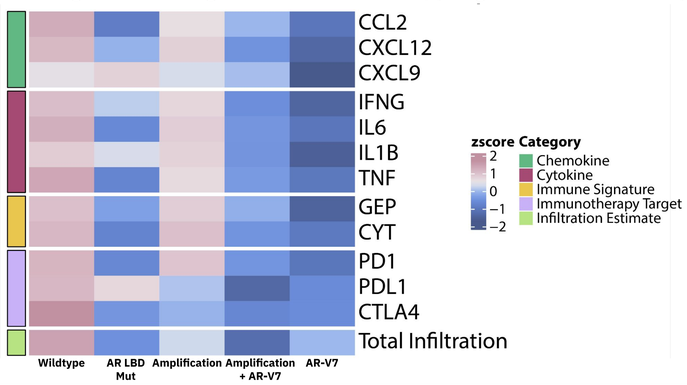

Figure 3. Heatmap showing the z-scores of various immune-related parameters across different CRPC subgroups. The value represent the mean of each parameter within each subgroup, normalized using z-scores for each row to highlight relative changes across the subgroups.

Figure 4. Forest Plot depicting the impact of AR mutations on total immune Infiltration in CRPC

Variable		N	Estimate	p
AR Mutation	Wildtype	478	Reference	
	Amplification	76	1.07 (−1.07, 3.20)	0.327
	AR–V7	177	−1.59 (−3.13, −0.06)	0.042
	Amplification+AR–V7	244	−4.05 (−5.44, −2.65)	<0.001
	AR LBD Mut	54	−1.92 (−4.47, 0.62)	0.138
TMB Level	Low	967	Reference	
	High	62	0.37 (−1.96, 2.69)	0.758
Tumor Purity		1029	−0.20 (−0.23, −0.16)	<0.001
Sample Collection Site	Male Genital Organs	235	Reference	
	Liver and Intrahepatic Bile Ducts	167	−1.96 (−3.71, −0.21)	0.028
	Bones, Joints, and Cartilage	117	−0.37 (−2.35, 1.61)	0.711
	Lymph Nodes	247	4.89 (3.28, 6.51)	<0.001
	Other	263	2.28 (0.70, 3.85)	0.005

Figure 4. Forest plot illustrating the outcomes of a multivariate regression model assessing the relationship between AR mutations and total immune infiltration, while controlling for tumor mutational burden (TMB) tumor purity and sample collection site. This model indicates a significant reduction in total immune infiltration associated the combination of AR amplification + Arv7.

Figure 5. Changes in immune infiltration in longitudinal samples

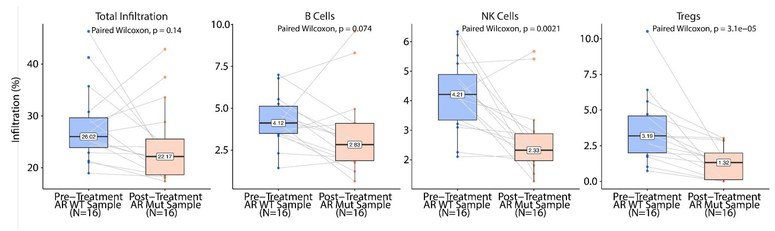

Figure 5. Paired box plots showing immune cell infiltration of total infiltration, B cells, NK cells and Tregs. Each plot compares pre-treatment AR wildtype samples with post-treatment of ADT/NHA AR mutant samples with in longitudinal cohort N=16 pairs). The x-axis represents two groups: pre-treatment (WT, blue) and post-treatment (AR mutant: Amplification, SNV or AR-v7, orange). The y axis quantifies immune cell infiltration levels for each sample. The paired lines illustrate the paired longitudinal samples. A general decrease in immune infiltration is observed in the post-treatment samples harboring gain of AR mutations. Statistically significance between groups was calculated using pairing wilcoxon test.

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