

Investigating Relationships amongst Intrinsic and Acquired Genomic Alterations on Overall Survival in Metastatic Prostate Cancer

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Introduction: Resistance to Androgen Receptor Pathway Inhibitors (ARPI) in metastatic prostate cancer (mPC) is universal and can be driven by complex genomic alterations. The evolution of lineage state transitions from adenocarcinomas to neuroendocrine prostate cancer (NEPC) has also been shown to drive treatment resistance and poor survival. Identifying the timing and association of genomic mutations with lineage state transitions has been limited by the requirement of serial tumor biopsies. We report an integrated analysis of clinical next-generation sequencing (NGS) data and mPC lineage states with a novel circulating tumor cell (CTC) RNA sequencing methodology.

Methods: We collected 273 samples from 117 unique patients with mPC in a prospective biomarker trial. CTCs were purified via immunomagnetic capture on an automated microfluidic technology and analyzed via RNA-seq. A subset of patients had a clinical grade genetic test performed on a contemporary metastatic tissue biopsy. We compared CTC gene expression for lineage states (luminal A, luminal B, NEPC) with somatic gene mutation subtypes known to confer resistance to ARPIs (AR, p53, RB, PTEN, HRR genes) and overall survival (OS).

Results: Single sample pathway analysis of high CTC purity samples identified four transcriptional phenotypes: luminal A-like (LumA), luminal B-like (LumB), low proliferation (LP), and neuroendocrine (NE). Compared to patients with low CTC burden/purity (median OS not reached), patients with LumA and LP phenotypes had similar survival, patients with LumB and NE CTC phenotypes had shorter survival (LumB: median OS 6m, HR 9.1[3.8-21.8], $p < 0.0001$, NE: median OS 3.7m, HR 11.8[2.4-57.2], $p = 0.0019$). *AR* alterations were found in samples with prior ARPI exposure and at similar frequencies across all CTC phenotypes but NE where they were absent. *RB* mutations were enriched in the unfavorable CTC phenotypes (LumB, NE; $p = 0.0288$). Integrating CTC phenotype with presence or absence of at least one high risk genomic alteration (*AR*, *RB*, *TP53*, *PTEN*), patients with favorable CTC phenotype (Low burden, LP and LumA) and no high risk alterations had the longest median survival (median OS NR), followed by patients with favorable phenotype but a high risk alteration (median OS 12.7m), patients with an unfavorable phenotype (LumB, NE) but no high risk alteration (median OS 8m), and unfavorable phenotype with a high risk alteration (median OS 4m).

Conclusions: Somatic mutations in mCRPC influence lineage state acquisitions and treatment resistance. Lineage state transitions themselves are associated with poor outcomes and decreased survival which is worsened in the presence of high-risk genetic mutations including RB. This data presents potentially targetable patient populations that would benefit from treatment intensification and early disease monitoring for more aggressive mCRPC subtypes.