Whole-Genome and Transcriptional Analysis of Treatment-Emergent Small-Cell Neuroendocrine Prostate Cancer Demonstrates Intraclasse Heterogeneity


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Background: Therapeutic resistance in metastatic castration-resistant prostate cancer (mCRPC) can be accompanied by treatment-emergent small-cell neuroendocrine carcinoma (t-SCNC), a morphologically distinct subtype.

Methods: We performed integrative whole-genome and -transcriptome analysis of mCRPC tumor biopsies including paired biopsies after progression, and multiple samples from the same individual.

Results: t-SCNC was significantly less likely to have amplification of AR or an intergenic AR-enhancer locus, and demonstrated lower expression of AR and its downstream transcriptional targets. Genomic and transcriptional hallmarks of t-SCNC included biallelic loss of RB1, elevated expression levels of CDKN2A and E2F1, and loss of expression of the AR and AR-responsive genes including TMPRSS2 and NKX3-1. We identified three tumors that converted from adenocarcinoma to t-SCNC and demonstrate spatial and temporal intrapatient heterogeneity of metastatic tumors harboring adenocarcinoma, t-SCNC, or mixed expression phenotypes, with implications for treatment strategies in which dual targeting of adenocarcinoma and t-SCNC phenotypes may be necessary.

Conclusions: The t-SCNC phenotype is characterized by lack of AR enhancer gain and loss of RB1 function, and demonstrates both interindividual and intraindividual heterogeneity.

Conflict of Interest
T.M Beer reports receiving commercial research grants from Alliance Foun- dation Trials, Boehringer Ingelheim, Clopset Therapeutics, Janssen Research & Development, Medivation/Astellas, OncoGenex, Soto, and Theracelon Sciences/Oncogenes, has ownership interest (including stock, patents, etc.) in Salarius Pharmaceuticals, and is a consultant/advisory board member for AbbVie, AstraZeneca, Pfizer, Astellas Pharma, Bayer, Boehringer Ingelheim, Clopset Oncology, GlaxoSmithKline, Janssen Biotech, Janssen Japan, and Merck. M.B. Rettig reports receiving commercial research grants from Novartis, Johnson & Johnson, and Astellas, has received speakers bureau honoraria from, and is a consultant/advisory board member for Johnson & Johnson. G.V Thomas is a consultant/advisory board member for Auron Therapeutics. P. Lloyd is an employee at Bluestar Genomics and has ownership interest (including stock, patents, etc.) in Bluestar Genomics, Pfizer, and Gilead. F.Y. Feng is co-founder at PFS Genomics and is a consultant/advisory board member for Astellas, Janssen, Sanofi, Bayer, Dendreon, Ferring, Celgene, and Blue Earth. J.J. Alumkal is a consultant/advisory board member for Astellas, Bayer, and Janssen. E.J. Small has ownership interest (including stock, patents, etc.) in Fortis Therapeutics and Harpoon Therapeutics and is a consultant/advisory board member for Janssen, Fortis Therapeutics, Harpoon Therapeutics, and Beigene. No potential conflicts of interest were disclosed by the other authors.

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