**Whole genomic copy number alterations in circulating tumor cells from men with abiraterone or enzalutamide resistant metastatic castration-resistant prostate cancer**

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**Background:** Beyond enumeration, circulating tumor cells (CTCs) can provide genetic information from metastatic cancer that may facilitate a greater understanding of tumor biology and enable a precision medicine approach.

**Methods:** CTCs and paired leukocytes from men with metastatic castration-resistant prostate cancer (mCRPC) were isolated from blood through red cell lysis, CD45 depletion, and flow sorting based on EpCAM/CD45 expression. We next performed whole genomic copy number analysis of CTCs and matched patient leukocytes (germline) using array-based comparative genomic hybridization (aCGH) from 16 men with mCRPC, including longitudinal and sequential CTCs aCGH analyses in the context of enzalutamide therapy.

**Results:** All patients had mCRPC and primary or acquired resistance to abiraterone acetate or enzalutamide. We compiled copy gains and losses, with a particular focus on those genes highly implicated in mCRPC progression and previously validated as being aberrant in metastatic tissue samples and genomic studies of reference mCRPC datasets. Genomic gains in >25% of CTCs were observed in AR, FOXA1, ABL1, MET, ERG, CDK12, BRD4, and ZFHX3, while common genomic losses involved PTEN, ZFHX3, PDE4DIP, RAF1, and GATA2. Analysis of aCGH in a sample with sequential enzalutamide resistant visceral progression showed acquired loss of AR amplification concurrent with gain of MYCN, consistent with evolution toward a neuroendocrine-like, AR-independent clone.

**Conclusions:** Genomic analysis of pooled CTCs in men with mCRPC suggests a reproducible, but highly complex molecular profile that includes common aberrations in AR, ERG, c-MET, and PI3K signaling during mCRPC progression, which may be useful for predictive biomarker development. Clinical validation of this CTC based genomic characterization in the context of enzalutamide or abiraterone acetate treatment response/resistance is ongoing in our PCF-Movember Global Treatment Sciences Challenge protocol across 5 DOD PCCTC sites (n=120), NCT02269982.

**Conflict of Interest**: Dr. Armstrong receives research funding and consulting fees with Medivation/Astellas and Janssen, Sanofi aventis, Dendreon, Bayer, Gilead. Research support from EPIC, PCF, DOD.

**Research Funding**: Prostate Cancer Foundation and Department of Defense Prostate Cancer Research Program Physician Research Training Award (Armstrong)