Chromosomal instability in diagnostic prostate needle biopsies predicts metastatic disease

Eric T. Miller[1], Sungyong You[3], Radu M. Cadaneanu[1], Sandy T. Liu[1], Xinmin Li[1], Lorna Kwan[1], Michael S. Lewis[2], Beatrice Knudsen[3], Michael R. Freeman[3], and Isla P. Garraway[1,2]*

[1]Department of Urology, Jonsson Comprehensive Cancer Center, David Geffen School of Medicine at UCLA, [2]Division of Urology, Greater Los Angeles VA Healthcare System, [3]Department of Pathology, Cedars-Sinai Medical Center

Background:
Genomic instability and treatment selection pressure likely contribute to the substantial heterogeneity observed in metastatic castration-resistant prostate cancer (mCRPC). While genomic profiling demonstrates phylogenic relationships of primary tumors and metastases that co-exist in heavily treated patients, characteristics of treatment-naïve metastatic precursors residing in the prostate remain poorly defined.

Methods:
Prostate cancer (PC) cases were identified from a racially and ethnically diverse cohort of men who were diagnosed and treated exclusively within a single Veterans Affairs (VA) healthcare system since the year 2000. Clinical annotation of the disease course was performed via electronic medical record abstraction and a cohort of clinical stage M0 or M1 at diagnosis were identified. Further sub-stratification was based upon metastatic tumor burden. Oligometastatic "oligo" disease was defined by $\leq$5 extrapelvic lymph node and/or bone metastases and no visceral metastases. Polymetastatic "poly" disease was defined as >5 metastases or any visceral involvement. Kaplan-Meier curves were generated to assess survival differences among sub-cohorts. Archival PNBX slides were annotated for Gleason grade and pathological features in a blinded fashion. High-grade PC was procured for RNA sequencing (RNAseq) and/or Oncoscan copy number alteration analysis from formalin-fixed and paraffin-embedded diagnostic prostate needle biopsies (PNBX) of 99 patients

Results:
Of 2134 patients that had follow-up information available, 121 displayed de novo metastases and 78 experienced metastatic progression. Kaplan-Meier curves demonstrated that polymetastatic cases had significantly shorter survival than oligometastatic cases. RNAseq of 99 high-grade cases, stratified by tumor burden (oligometastatic, polymetastatic, or no metastatic progression), revealed distinct transcriptomic profiles. In polymetastatic disease, proliferation and chromosomal instability (CIN) genes were enriched and associated with significant copy number alterations. A 157-gene metastasis signature, identified by comparing PNBX transcriptome data with mCRPC datasets from previously published studies, separated metastatic and non-metastatic cases. Seven CIN genes (CIN7) nested within the 157-gene signature accurately predicted the emergence of clinical metastases in men originally diagnosed with high-grade localized disease. CIN7 also predicted adverse outcomes in two independent prostate cancer cohorts.

Conclusions: We have illuminated a transcriptomic footprint of mCRPC in pretreatment diagnostic prostate needle biopsies (PNBX) of men with de novo metastases or localized disease with eventual metastatic progression. Our study establishes that mCRPC biological features are embedded in untreated primary tumors of men who experience metastatic progression, are detectable in diagnostic PNBX, and prognostic of adverse outcomes.

Conflict of Interests: None to disclose.

Funding Acknowledgements: DOD PC131996, PCF-Movember GAP1 Unique TMAs Project, Prostate Cancer Foundation (PCF) Creativity Award, Jean Perkins Foundation, NIH/NCI P01 CA098912-09, NIH R01CA131255 and P50CA092131, Stephen Spielberg Team Science Award.