

## **Integrated radiologic, genomic and pathologic analysis revealed intratumoral divergent responses to neoadjuvant anti-androgen therapy**

**Scott Wilkinson**<sup>1</sup>, Huihui Ye<sup>2</sup>, Nicholas T. Terrigino<sup>1</sup>, Nicole Carrabba<sup>1</sup>, Rayann Atway<sup>1</sup>, Shana Y. Trostel<sup>1</sup>, John R. Bright<sup>1</sup>, S. Thomas Hennigan<sup>1</sup>, Rosina T. Lis<sup>3</sup>, Ross Lake<sup>1</sup>, Stephanie Harmon<sup>1</sup>, Baris Turkbey<sup>1</sup>, Peter A. Pinto<sup>1</sup>, Peter L. Choyke<sup>1</sup>, Fatima Karzai<sup>1</sup>, David J. VanderWeele<sup>1</sup>, Kathleen Kelly<sup>1</sup>, William L. Dahut<sup>1</sup>, and Adam G. Sowalsky<sup>1</sup>

<sup>1</sup>National Cancer Institute, NIH, Bethesda, MD, 20892

<sup>2</sup>Department of Pathology, UCLA, Los Angeles, CA, 90095

<sup>3</sup>Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, 02215

### **Background:**

Localized prostate cancers are uniquely genetically variable, comprising both spatially separate regions and multiple independently evolving clones within each region. The multifocality of prostate cancer is a well-acknowledged problem for diagnosis, and the differential aggressiveness of potentially independent clones remains largely unknown. Further, appropriate prostate cancer staging using multiparametric MRI (mpMRI) and biopsy tissue can be confounded by sampling error. To date, there has been no understanding of whether this variability influences management decisions for localized prostate tumors. Here, we sought to identify the sensitivity and genomic profile of distinct localized tumors from a single patient following systemic intense neoadjuvant androgen deprivation therapy.

### **Methods:**

A 66-year-old man with high risk prostate cancer was enrolled onto a Phase 2 study of neoadjuvant androgen deprivation therapy plus enzalutamide. mpMRI was performed at baseline, showing a single semi-contiguous lesion encompassing the right apical-mid peripheral zone also extending into the left distal apical peripheral zone. MR/ultrasound-fusion targeted biopsy was performed before undergoing 6 months of intense neoadjuvant androgen deprivation therapy (goserelin and enzalutamide). Biopsies of the left- and right-sided tumors showed differing histologies. A second mpMRI was performed following therapy before radical prostatectomy. Laser capture microdissection was performed to isolate pure populations of tumor cells from the pre-treatment biopsy and post-treatment surgical specimen. Whole exome sequencing was performed on microdissected tissues to identify somatic mutations and copy number alterations, which were further used to assess tumor clonal architecture and genomic/phenotypic evolution of treatment resistant tumor.

### **Results:**

After six months of systemic therapy and radical prostatectomy, mpMRI and pathology showed near complete response of one tumor and substantial resistance of the other tumor, which exhibited a large intraductal component. Histopathological staining and whole exome data highlighted a divergence in the status of tumor suppressor genes implicated in prostate cancer progression, with the non-responding tumor at baseline exhibiting additional alterations absent from the pre-treatment tumor that responded to therapy. Using point mutations as definitive clonal markers, we found that two clonally-independent tumors exhibited intrinsic heterogeneity at baseline which correlated with response or resistance.

### **Conclusions:**

These data highlight that even nascent prostate cancer is heterogenous and neoadjuvant therapeutic strategies will need to consider this for clinical optimization. Evolutionary trajectories that resulted in tumor heterogeneity in this case likely contributed to our observation that two independent prostate tumor nodules with distinct genetic alterations responded differently to neoadjuvant intense ADT.

### **Conflicts of Interest:**

Huihui Ye: Janssen (consulting)

### **Funding Acknowledgments:**

This work was supported by the Intramural Research Program of the NIH, National Cancer Institute, the Prostate Cancer Foundation, and Department of Defense Prostate Cancer Research Program (W81XWH-19-1-0712 to S.W., W81XWH-16-1-0433 to A.G.S.).