Prostate cancer neoadjuvant intensive androgen deprivation therapy selects for tumor foci with diverse oncogenic alterations

Adam G. Sowalsky1, Huihui Ye2, Manoj Bhasin2, Eliezer M. Van Allen3, Massimo Loda4, Rosina T. Lis4, Laleh Montaser2, Carla Calagua2, Fen Ma2, Joshua W. Russo2, Rachel J. Schaefer2, Olga S. Voznesensky2, Zhenwei Zhang3, Glenn J. Bubley2, Robert B. Montgomery5, Elahe A. Mostaghel5, Peter S. Nelson5, Mary-Ellen Taplin1, Steven P. Balk2

1National Cancer Institute, NIH, Bethesda, MD, 20892
2Beth Israel Deaconess Medical Center, Boston, MA 02215
3Dana-Farber Cancer Institute, Boston, MA 02215
4Brigham and Women’s Hospital, Boston, MA 02215
5University of Washington, Seattle, WA, 98105

Background:
Based on the hypothesis that early use of androgen deprivation therapy (ADT) may improve outcomes, we conducted a phase 2 trial of neoadjuvant leuprolide for 24 weeks in combination with abiraterone acetate and prednisone (referred to subsequently as leuprolide plus abiraterone) for 12 or 24 weeks prior to radical prostatectomy (RP). As reported recently, we confirmed that the addition of abiraterone further markedly reduced intraprostatic androgen levels and appeared to improve responses relative to historical controls using single agent GnRH agonists. Nonetheless, residual prostate cancer (PCa) was found in the majority of patients, with only a small number of patients demonstrating complete pathological responses. Moreover, substantial nuclear and cytoplasmic AR expression was detected by immunohistochemistry in most cases, suggesting that AR activity still may persist and contribute to residual disease.

Methods:
Residual PCa foci in RPs from 18 men treated with neoadjuvant intensive androgen deprivation therapy (leuprolide, abiraterone acetate, prednisone) were microdissected and analyzed for resistance mechanisms.

Results:
Transcriptome profiling showed reduced but persistent androgen receptor (AR) activity in residual tumors, with no increase in neuroendocrine differentiation. Unexpectedly, proliferation was negatively correlated with AR activity, but positively correlated with decreased RB1 expression, and whole exome sequencing (WES) further showed enrichment for RB1 genomic loss. In 14 cases where 2 tumor foci were microdissected, WES confirmed a common origin, but identified multiple oncogenic alterations unique to one focus.

Conclusions:
Primary PCa can have extensive microheterogeneity, but its contribution to the later emergence of metastatic castration-resistant PCa (mCRPC) has not been clear. These findings indicate that therapy selects for subclonal genomic alterations, including RB1 loss, which may be the origin for metastatic castration-resistant PCa, and are selected for by neoadjuvant intense androgen deprivation therapy. This study indicates that subclonal RB1 loss may be more common than previously appreciated in intermediate to high risk primary PCa, and may be an early event, independent of neuroendocrine differentiation, in the development of mCRPC. Comprehensive molecular analyses of primary PCa may detect aggressive subclones, and possibly inform on adjuvant strategies to prevent the emergence of mCRPC.

Conflicts of Interest: Mary-Ellen Taplin is a member of the Advisory Board for Janssen Pharmaceutica and receives research funding from Janssen Pharmaceutica. Other authors have no conflict of interest.

Funding Acknowledgments: This work was supported by NIH grants (DH/HCC SPORE P50 CA090381 to A.G.S., M.L., and S.P.B., Pacific Northwest SPORE P50 CA097186 to P.S.N., P01 CA163227 to S.P.B.), the Prostate Cancer Foundation (Challenge Awards to P.S.N./S.P.B. and M.E.T./R.B.M., Young Investigator
Awards to A.G.S., H.Y., E.V.M., and E.A.M.), Department of Defense Prostate Cancer Research Program (W81XWH-13-1-0267 and W81XWH-16-1-0433 to AGS; W81XWH-16-1-0431 to S.P.B. and W81XWH-16-1-0432 to M.E.T.) and the Intramural Research Program of the NIH, National Cancer Institute. The original abiraterone COU-AA-201 study was funded by Janssen Research & Development.