Results of a phase II trial of neoadjuvant abiraterone + prednisone+ enzalutamide + leuprolide (APEL) versus enzalutamide + leuprolide (EL) for patients with high-risk localized prostate cancer (PC) undergoing radical prostatectomy (RP)

Authors:
Rana R. McKay[1, 2]
Wanling Xie[2]
Rosina Lis[2]
Hui-Hui Ye[3]
Zhenwei Zhang[2]
Quoc-Dien Trinh[2]
Steven L. Chang[2]
Lauren C. Harshman[2]
Ashley E. Ross[4]
Kenneth J. Pienta[4]
Daniel W. Lin[5]
William J. Ellis[5]
Bruce Montgomery[5]
Peter Chang[3]
Andrew A. Wagner[3]
Glenn J. Bubley[3]
Adam S. Kibel[2]
Mary-Ellen Taplin[2]

[1]University of California, San Diego, San Diego, CA
[2]Dana-Farber Cancer Institute and Brigham & Women's Hospital, Boston, MA
[3]Beth Israel Deaconess Medical Center, Boston, MA
[4]Johns Hopkins Hospital, Baltimore, MD
[5]University of Washington, Seattle, WA

First Author Contact Information:
Rana R. McKay, MD
Assistant Professor of Medicine
University of California, San Diego
3855 Health Sciences Drive, #0987
La Jolla, CA 92093-0987
Phone: (858) 822-6185
Fax: (858) 822-6220
rmckay@ucsd.edu

Conflicts of Interest: RRM received research funding from Bayer, Pfizer, and Genentech and serves on the Advisory Board for Janssen, Novartis and Tempus. HY serves on the Advisory Board for Janssen. ASK serves on the Advisory Board for Janssen, Pfizer, Insight, and Profound. MET has served on the Advisory Boards for Janssen and Medivation/Astellas and has received clinical research funding from Medivaton/Astellas and Janssen. The remaining authors have no disclosures.

Funding Acknowledgments: Clinical trial support was provided by Astellas/Medivation. Additional support from the Fairweather Family Fund and Fat Boys Slim Sisters PMC Fund at the Lank Center for GU Oncology Dana-Farber Cancer Institute (MET), Prostate Cancer Foundation Challenge Award 16CHAS03, 142016 (MET), Prostate Cancer Clinical Trials Consortium (MET), Prostate Cancer Foundation Young Investigator Award (HY), and the DF/HCC Prostate Cancer SPORE (NCI P50 CA090381).

Background:
Patients with high-risk PC have an increased risk of recurrence and mortality despite therapy. Abiraterone, a CYP17 inhibitor, and enzalutamide, a next generation anti-androgen, have demonstrated improved overall survival in metastatic PC. In this multicenter randomized phase II trial, we evaluate the impact of second generation hormone therapy on RP pathologic outcomes.

Methods:
Eligible patients had biopsy Gleason score ≥4+3=7, PSA >20 ng/mL or cT3 disease (by prostate MRI). Lymph nodes were required to be <20 mm. Patients were randomized 2:1 to APEL:EL for 6 cycles (24 weeks) followed by RP. All RPs underwent central pathology review. The primary endpoint was the rate of pathologic complete response (pCR) or minimum residual disease (MRD, tumor ≤5 mm); compared between arms with Fisher's exact test, with two-sided p≤0.20 considered significant. Secondary endpoints include PSA response, surgical staging at RP, positive margin rate, and safety. Biomarkers associated with pathologic outcomes were explored.

Results:
Seventy-five patients were enrolled at four sites: DFCI/BWH (n=55), BIDMC (n=11), UW (n=5), JHU (n=4). Median age was 62 years. Most patients had NCCN high-risk disease [n=66, 88%; cT3 n=21 (28%), Gleason 8-10 n=59 (79%), PSA >20 ng/mL n=17 (23%)]. All patients completed 6 cycles followed by RP. Median PSA nadir was 0.03 and 0.02 ng/mL and time to nadir was 3.7 and 4.6 months in the APEL and EL arms, respectively. The combined pCR or MRD rate was 30% (n=15/50) in the APEL arm and 16% (n=4/25) in the EL arm. The response difference was 14% (80% CI -3%-30%, p=0.263). Fifteen patients (14 in APEL; 1 in EL) had grade 3 adverse events (AEs). The most common grade 3 AEs were hypertension (n=7) and ALT increase (n=5). No grade 4-5 AEs occurred. Residual tumors in the two arms showed comparable levels of ERG, PTEN, AR and PSA expression. Tumor ERG positivity and PTEN-loss were associated with more extensive residual tumors at RP.

Conclusions:
Neoadjuvant hormone therapy plus RP in men with high-risk PC resulted in favorable pathologic responses (≤5 mm residual tumor) in 16-30% with a trend towards improved pathologic outcomes with APEL and acceptable safety profile. Follow-up is necessary to evaluate the impact of therapy on recurrence rates. The potential association of ERG and PTEN alterations with worse outcomes warrants further investigation.

Table 1. Pathologic outcomes at RP.

	APEL (n=50)	EL (n=25)	Total (n=75)
pT2	40%	36%	39%
pT3	50%	56%	52%
Positive Margins	18%	12%	16%
Seminal Vesicle Involvement	18%	28%	21%
Lymph Node Involvement	10%	12%	11%
pCR	10%	8%	9%
MRD	20%	8%	16%