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)

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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.

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