Background

- Metastatic castration-resistant prostate cancer (mCRPC) remains at the forefront of urology in 2021, despite the availability of multiple classes of therapies that delay disease progression and prolong patient survival.

- Androgen receptor (AR) signaling is a key driver of tumor growth in mCRPC, and those patients who progress on or after enzalutamide are the mainstay for patients with locally advanced or metastatic disease.

- Exicorilant (UNM-2200) is an AR antagonist, currently used, but resistance typically develops within 6–12 months.1

- The glucocorticoid receptor (GR) antagonist can provide a tumor escape pathway following anti-androgen therapy by becoming the dominant growth factor.2

- GR expression in prostate cancer is associated with poor clinical outcomes.

- Exicorilant + castration significantly reduced tumor growth and improved progression-free survival (PFS) in patients with mCRPC (NCT03479414).

Exicorilant (CORT125821)

- A competitive, reversible, full antagonist of GR (K1 and IC50 ~15 nM in human GR binding and functional assay with selectivity for GR relative to other hormone receptors6).

- In mouse 22Rv1 prostate cancer xenografts:
  - Exicorilant + castration significantly reduced tumor growth compared to castration alone (P<0.001, left).
  - Exicorilant + enzalutamide significantly reduced tumor growth compared to enzalutamide alone in castrated mice (P<0.02; right).

Summary & Conclusions

- There is an unmet need for novel, targeted treatments that can overcome tumor escape pathways to existing therapies in mCRPC.

- This is the first study of the selective GR modulator exicorilant in combination with enzalutamide in patients with mCRPC.

- Exicorilant 240 mg QD + enzalutamide 160 mg QD was selected as the phase 2 regimen.

- The most clinically relevant AEs were nausea, abdominal pain, and decreased appetite.

- No clinically relevant changes in enzalutamide exposures were observed when combined with exicorilant vs. enzalutamide alone.

- Cortisol and ACTH were not significantly altered by exicorilant.

- Further pharmacodynamic and efficacy results will be presented in the future.

Pharmacokinetics & Pharmacodynamics: Segments 1 & 2

Segment 1: Enzalutamide PK in the Presence/Abstinence of Exicorilant

- Mean AUC and Cmax of enzalutamide following the once-daily dosage of enzalutamide on CORT1-10 were used to estimate the need for enzalutamide drug interaction (DDI).

- CORT1-10: Day 8 of enzalutamide monotherapy lead-in (CORT1-30): Day 9 of combined therapy

- Mean ratios ± 0.25 or ± 0.14 are considered indicative of no clinically relevant DDI

- Therefore, no exicorilant dose modification was warranted upon coadministration with exicorilant.

- Enzalutamide exposures were largely overlapping across arms, irrespective of enzalutamide dose level, and consistent with historical data for enzalutamide 160 mg alone.1

Segment 2: Exicorilant & Exicorilant-Related AEs

- Exicorilant exposures were largely overlapping across arms and dose levels.

- Greater increases in AUC were observed following dose escalation from 240 mg to 320 mg QD. DLTs were observed.

- The mean Cmax was similar at the 280 mg and 320 mg doses.

- Exicorilant does not affect ACTH or Cortisol Levels

- Combination of exicorilant and enzalutamide is not associated with any increase in glucocorticoid hormone levels.

- Modulation of GR Target Genes Observed

- CBNGC is an established glucocorticoid-inducible gene with important roles in regulating cell growth.

- CBNGC was suppressed in blood after 2 weeks of exicorilant treatment in Segment 1 with enzalutamide 160 mg (paired T-test: P<0.001).

5 Segment 2 Dose Selection

Baseline Demographics & Disease Characteristics

<table>
<thead>
<tr>
<th>Arm</th>
<th>N</th>
<th>Age (yrs)</th>
<th>ECOG Performance Status</th>
<th>Race</th>
<th>Gender</th>
<th>Baseline PSA (mg/L)</th>
<th>Bone Only</th>
<th>Mean Time to Disease Progression (months)</th>
<th>Disease Site, n (%), Listed (Range)</th>
<th>LMP/EM/SP</th>
<th>Shrinkage</th>
<th>Progression</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm A</td>
<td>10</td>
<td>75.2 (66-84)</td>
<td>0.0</td>
<td>White</td>
<td>Male</td>
<td>20.0 (10.0-29.0)</td>
<td>80.0</td>
<td>24.0 (16.0-30.0)</td>
<td>Hormonal (40.0%), Progression 40.0%</td>
<td>22.0 (16.0-30.0)</td>
<td>14.0 (12.0-16.0)</td>
<td>80.0</td>
<td>14.0 (12.0-16.0)</td>
</tr>
<tr>
<td>Arm B</td>
<td>10</td>
<td>75.2 (66-84)</td>
<td>0.0</td>
<td>White</td>
<td>Male</td>
<td>20.0 (10.0-29.0)</td>
<td>80.0</td>
<td>24.0 (16.0-30.0)</td>
<td>Hormonal (40.0%), Progression 40.0%</td>
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2 The authors thank all those who participated in this study. The study patients and their families, the investigators, and the sponsor team.

References