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Phase 1 Results of Exicorilant+Enzalutamide in Patients with Castration-Resistant Prostate Cancer

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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 fatigue and pain in leg/extremity consistent with neuropathic pain.
  - Modulation of a GR-regulated gene was observed.
- 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.

Speaker Disclosures

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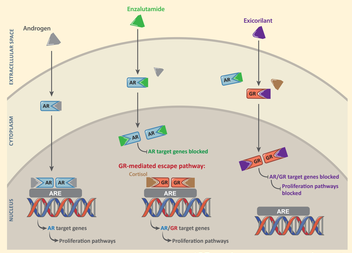
Background

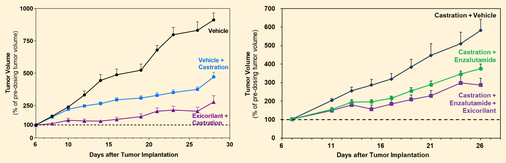
- Metastatic castration-resistant prostate cancer (mCRPC) remains an incurable disease, despite the availability of multiple classes of therapies that delay disease progression and prolong life.[1]
- Androgen receptor (AR) signaling is a key driver of tumor growth in mCRPC, and AR-targeted therapies are the mainstay for patients with locally advanced or metastatic disease.
  - Enzalutamide[2,3], an AR antagonist, is commonly used, but resistance typically develops within 8-12 months.[3,4]
- The glucocorticoid receptor (GR) can provide a tumor escape pathway following anti-androgen therapy by becoming the dominant growth factor.[5]
  - GR expression in prostate cancer is associated with poor clinical outcomes.[5]
- Combining the selective GR modulator (SGRM) exicorilant with enzalutamide may block this escape pathway via dual antagonism of GR and AR.



ARE, androgen response element.

Exicorilant (CORT125281)

- A competitive, reversible, full antagonist of GR (K <1 and IC_{50}<15 nM in human GR binding and functional assays) with selectivity for GR relative to other hormone receptors[6]
- In mouse 22Rv1 prostate cancer xenograft models:
  - Exicorilant + castration significantly reduced tumor growth compared to castration alone (*P*<0.0001, left).
  - Exicorilant + enzalutamide significantly reduced tumor growth compared to enzalutamide alone in castrated mice (*P*=0.02, right).



Left: N=10 mice/group. Castration performed 5 days after inoculation with 22Rv1 tumor cells; exicorilant treatment initiated on day 6 for 21 days. **Right:** N=10 mice/group. Castration performed 3 days before implantation of 22Rv1 tumor cells; exicorilant & enzalutamide treatment initiated on day 7 for 21 days.

- Here, we report safety, tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) results from the first study of exicorilant + enzalutamide in patients with mCRPC (NCT03437941).

1 Study Design: Segments 1 & 2

- **Primary endpoint:** Identify a phase 2 dose of exicorilant + enzalutamide
- **Secondary endpoints:** Safety, PK, PD, and preliminary anti-tumor efficacy of the combination
- **Patient population:** Patients with mCRPC with or without rising prostate-specific antigen (PSA; 25% increase over nadir and absolute value >1 ng/mL)
- Enzalutamide administered once daily in both segments (Segment 1: 160 mg; Segment 2: at currently tolerated, stable dose)
- **Exicorilant dosing schedules:**

  Segment 1: Exicorilant (140 or 180 mg) given twice daily, fasted

  Standard '3+3' design, including 1 cohort with a 28-day enzalutamide monotherapy lead-in preceding cycle 1 of exicorilant + enzalutamide

  Segment 2: Exicorilant given once daily, with food

  Double-blind design: Patients randomized 3:1 to exicorilant titration or to stay on exicorilant and receive placebo

2 Baseline Demographics: Segment 1 & 2

	Segment 1 (N=12)	Segment 2 (N=25)	Total (n=37)
Age, median (range), years	69.5 (53, 80)	71.0 (53, 82)	70.0 (53, 82)
≥65 years, n (%)	8 (66.7%)	15 (60.0%)	23 (62.2%)
ECOG performance status, n (%)			
0	8 (66.7%)	13 (52.0%)	21 (56.8%)
1	4 (33.3%)	12 (48.0%)	16 (43.2%)
Prior lines of AR pathway inhibitor, n (%)			
0	7 (58.3%)	0	7 (18.9%)
1	2 (16.7%)	18 (72.0%)	20 (54.1%)
≥2	3 (25.0%)	7 (28.0%)	10 (27.0%)
Prior lines of taxanes, n (%)			
0	6 (50.0%)	12 (48.0%)	18 (48.6%)
1	3 (25.0%)	13 (52.0%)	16 (43.2%)
2	3 (25.0%)	0	3 (8.1%)

2 enrolled patients did not receive exicorilant and are not included in this table.

3 Safety: Segments 1 & 2

	Segment 1 (N=12)	Segment 2 (N=25)	Total (n=37)
Back pain	7 (58.3%)	17 (68.0%)	24 (64.9%)
Fatigue	6 (50.0%)	16 (64.0%)	22 (59.5%)
Constipation	4 (33.3%)	10 (40.0%)	14 (37.8%)
Decreased appetite	4 (33.3%)	7 (28.0%)	11 (29.7%)
Pain in extremity	3 (25.0%)	6 (24.0%)	9 (24.3%)
Anemia	0	8 (32.0%)	8 (21.6%)
Abdominal pain	3 (25.0%)	5 (20.0%)	8 (21.6%)
Lipase increased	0	8 (32.0%)	8 (21.6%)
Arthralgia	2 (16.7%)	5 (20.0%)	7 (18.9%)
Nausea	2 (16.7%)	5 (20.0%)	7 (18.9%)
Weight decreased	3 (25.0%)	3 (12.0%)	6 (16.2%)

Treatment-emergent adverse events (TEAEs) of any grade reported in >15% of patients. There was 1 grade 4 TEAE unrelated to exicorilant (sepsis) and no grade 5 TEAEs.

- 2/12 (16.7%) patients in Segment 1 reported serious adverse events (SAEs) related to exicorilant: Acute pancreatitis (n=1); fatigue and musculoskeletal pain (n=1).

4 Pharmacokinetics & Pharmacodynamics: Segments 1 & 2

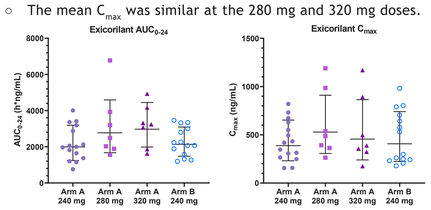
Segment 1: Enzalutamide PK in the Presence/Absence of Exicorilant

- Mean ratios of enzalutamide + N-desmethyl enzalutamide exposures on C2D1 / C1D-1 were used to assess the potential drug-drug interaction (DDI).
  - C1D-1: Day 28 of enzalutamide monotherapy lead-in
  - C2D1: Day 29 of combined therapy
  - Mean ratios <0.75 or >1.4 are considered indicative of a notable DDI and require dose modification to achieve target exposures.
- The observed mean ratios of 1.14 for C_{max} and 1.26 for AUC were considered indicative of no notable DDI.
- Therefore, no enzalutamide dose modification was warranted upon coadministration with exicorilant.

C_{max}, maximum concentration; AUC, area under the curve; CxDy, cycle x day y.

Segment 2: Enzalutamide & Exicorilant Exposures

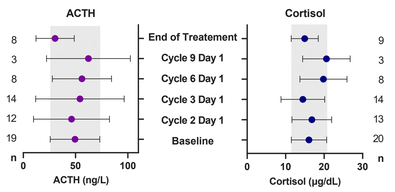
- **Exicorilant exposures** were largely overlapping across arms and dose levels.
  - Greater increases in AUC were observed following dose escalation from 240 mg to 280 mg vs. 280 mg to 320 mg.
  - The mean C_{max} was similar at the 280 mg and 320 mg doses.



- **Enzalutamide exposures** were largely overlapping across arms, irrespective of exicorilant dose level, and consistent with historical data for enzalutamide 160 mg alone.[7]

Exicorilant Does Not Affect ACTH or Cortisol Levels

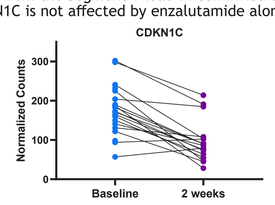
- Consistent with prior studies of exicorilant and other SGRMs[8], morning serum cortisol and ACTH levels were not affected by exicorilant.



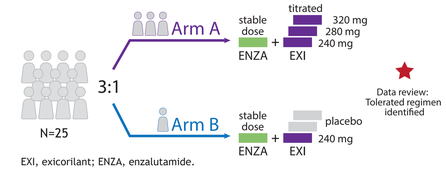
Showing mean ± SD in the safety population (all patients who received at least 1 dose of exicorilant). Gray band: Baseline mean ± SD. ACTH, adrenocorticotropic hormone; SD, standard deviation.

Modulation of GR Target Genes Observed

- CDKN1C is an established glucocorticoid-inducible gene with important roles in regulating cell growth.[9]
- CDKN1C was suppressed in blood after 2 weeks of dosing with exicorilant 240 mg + enzalutamide 160 mg (paired T-test *P*<0.0001).
- Data from the Segment 1 lead-in confirmed that CDKN1C is not affected by enzalutamide alone.



5 Segment 2 Dose Selection



EXI, exicorilant; ENZA, enzalutamide.

Baseline Demographics & Disease Characteristics

	Arm A (EXI 240-320 mg + ENZA) (n=19)	Arm B (EXI 240 mg + ENZA) (n=6)	Segment 2 Total (n=25)
Disease site, n (%)			
Lung and/or liver	4 (21.1%)	1 (16.7%)	5 (20.0%)
Bone only	6 (31.6%)	2 (33.3%)	8 (32.0%)
No measurable disease	0	1 (16.7%)	1 (4.0%)
Median PSA level, ng/mL, median (range)	16.3 (3.2, 2300)	14.3 (6.4, 47.2)	16.3 (3.2, 2300)
Prior AR-pathway inhibitor, n (%)	19 (100.0%)	6 (100.0%)	25 (100.0%)
Abiraterone	4 (21.1%)	2 (33.3%)	6 (24.0%)
Apalutamide	1 (5.3%)	0	1 (4.0%)
Enzalutamide	19 (100.0%)	6 (100.0%)	25 (100.0%)
Prior taxane, n (%)	9 (47.4%)	4 (66.7%)	13 (52.0%)
Cabazitaxel	1 (5.3%)	0	1 (4.0%)
Docetaxel	8 (42.1%)	4 (66.7%)	12 (48.0%)
Median treatment duration, weeks (range)	6.1 (2, 61)	19.5 (10, 42)	9.7 (2, 61)

TEAEs

- TEAEs leading to exicorilant discontinuation: Fatigue (n=3); back pain, pain in extremity (n=2 each); groin pain (n=1)
- 4/25 (16%) patients in Segment 2 reported SAEs: Back pain (n=2), sepsis, confusional state, urinary retention, pelvic pain (n=1 each)
  - Only 1 SAE was assessed as related to exicorilant (back pain).
  - No SAEs with fatal outcome were reported.
- Reports of pain in extremity (leg, feet) and sensory neuropathy (legs, feet, toes) were indicative of neuropathic pain.
- TEAEs of fatigue and back pain, while consistent with enzalutamide treatment and underlying disease, were exacerbated by combination treatment with exicorilant.
- Segment 2 patient disposition:
  - As of July 7, 2022, 3/25 patients were still receiving exicorilant.
  - Most patients discontinued exicorilant due to disease progression or AE.

	All Segment 2 Patients (N=25)	
	Grade 3	All Grades
Patients with any exicorilant-related TEAE, n (%)	23 (92.0%)	
Fatigue	3 (12.0%)	16 (64.0%)
Back pain	2 (8.0%)	10 (40.0%)
Decreased appetite	–	6 (24.0%)
Pain in extremity	–	5 (20.0%)
Constipation	–	7 (28.0%)
Lipase Increased	2 (8.0%)	7 (28.0%)
Nausea	–	5 (20.0%)
Abdominal pain	–	5 (20.0%)
Anemia	–	4 (16.0%)
ALT increased	2 (8.0%)	3 (12.0%)

Exicorilant-related TEAEs reported in >15% of patients and grade 3 exicorilant-related TEAEs reported in >1 patient. There were no grade 4 or 5 exicorilant-related AEs. ALT, alanine aminotransferase.

Dose-limiting Toxicities (DLTs)

- DLTs were recorded from the first exicorilant dose through cycle 3.
- DLTs of lipase increase and increased liver enzymes were transient and resolved with study drug interruption.
- Exicorilant 240 mg QD + enzalutamide 160 mg QD was selected as the phase 2 dose based on DLTs.

	DLT-evaluable Patients	Patients with ≥1 DLT	DLT
Segment 2, n (%)	16	6 (37.5)	
Arm A	10	5 (50.0%)	
EXI 240 mg + ENZA	4	4 (100.0%)	Lipase elevation/increase (n=3); fatigue, increased ALT (n=2 each); elevated AST, increased GGT, worsening back pain, hypophosphatemia (n=1 each)
EXI 280 mg + ENZA	1	1 (100.0%)	Back pain, vomiting (n=1 each)
EXI 320 mg + ENZA	5	0	–
Arm B			
EXI 240 mg + ENZA + Placebo	6	1 (16.7%)	Fatigue

AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase.

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