Prostate cancer is the second leading cause of cancer-related death in men. Second-generation antiandrogens such as enzalutamide and abiraterone benefit patients with castration-resistant prostate cancer (CRPC). However, relapse eventually occurs (Giacinti S et al, 2018).

The glucocorticoid receptor (GR) has been identified as a potential antiandrogen bypass mechanism, and thus GR inhibition may overcome this resistance to restore or prolong antiandrogen sensitivity (Arora V et al, 2013, Isikbay M et al, 2014).

- **ORIC-101** is a selective and potent GR antagonist without androgen receptor (AR) agonism, making this compound particularly suitable for combination with enzalutamide (Rew Y et al, 2018).
- **ORIC-101** showed good safety, pharmacokinetic properties, and target engagement in phase 1a healthy volunteer studies.
- A phase 1b study of ORIC-101 in combination with enzalutamide is planned in patients with metastatic prostate cancer.

---

**ORIC-101 is a selective and potent GR antagonist**


---

**GR is widely expressed in prostate tumors**

A and B. AR and GR mRNA (A) and protein (B) levels in prostate cancer cell lines. C and D. GR (relative to GRs line OV-CaSAR) and AR (relative to ARs line LNCaP) mRNA levels in prostate tumor organoids. E. GR immunohistochemistry detecting GR protein levels in human prostate tumor tissue.

---

**ORIC-101 reverses GR-driven resistance to enzalutamide in CRPC cells**

A. Microscopy images of CWR22PC and VCaP cells under the indicated treatment conditions for 3 weeks. B. Cell numbers of CWR22PC + ORIC-101 vs. A. Cell numbers of CWR22PC cells in A. Veh., vehicle; Enz: 2 μM enzalutamide; Dex: 30 nM dexamethasone; R1881: 100 μM synthetic AR ligand; 101: 0.5 μM ORIC-101; d: days; assay was done in C5SS media.

---

**CONCLUSIONS**

- GR is widely expressed in prostate tumor cell lines, organoids, and tissues.
- AR inhibition leads to enhanced GR levels at mRNA and protein levels.
- GR levels correlate with glucocorticoid-driven CRPC viability.
- ORIC-101 reverses GR-driven resistance to enzalutamide in CRPC cells and organoids.
- FKBP5 and KLK3 are rational pharmacodynamic biomarkers that may be evaluated in clinical studies of ORIC-101 in CRPC.