2. GR Activation is Induced by AR/AKT Blockade

GR protein levels and the expression of GR and target genes are significantly upregulated upon 7-day treatment with enzalutamide. Elevated GR levels and activity are sustained with the combination of enzalutamide and an AKT inhibitor GDC-0068 (MK-2206, or AZD5363), in PTEN-null LNCaP and PTEN-wildtype CWR22PC cells.

3. ORIC-101 Reverses GR-driven Resistance to AR/AKT Blockade in PTEN-wildtype CWR22PC Cells

Co-treatment with enzalutamide and an AKT inhibitor blunts androgen-induced cell growth. PSA secretion, and androgen-regulated gene expression. GR activation with glucocorticoids partially restores cell growth. PSA secretion and gene expression in the presence of AR/AKT blockade. This resistance is completely reversed by ORIC-101. The combination of enzalutamide with GR antagonist ORIC-101 reverses GR-mediated resistance to AR/AKT blockade.

4. ORIC-101 Reverses GR-driven Resistance to AR/AKT Blockade in PTEN-null LNCaP Cells

The combination of AKT inhibitor GDC-0068 with abiraterone was found to significantly prolong radiographic-progression-free survival over placebo with abiraterone in a PHOCUS randomized controlled trial (Fizazi et al., 2020). We confirmed in PTEN-null LNCaP that GR activation partially restored cell viability allowing escape from AR/AKT blockade, which was completely reversed by ORIC-101.

CONCLUSIONS

- GR upregulation and activation drives resistance when androgens are combined with an AKT inhibitor in preclinical studies
- GR antagonist ORIC-101 overcomes GR-driven resistance to the combination of enzalutamide and AKT inhibitor and restores antitumor activity in preclinical prostate cancer models
- Rescue by ORIC-101 is observed in both PTEN wildtype and PTEN-null prostate cancer models

The combination of enzalutamide with GR antagonist ORIC-101 is being studied in patients with metastatic CRPC (Phase Ib, NCT03923236)