GR Antagonist ORIC-101 Overcomes GR-mediated Resistance to the Combination of AR and AKT Inhibition in Preclinical Prostate Cancer Cell Lines

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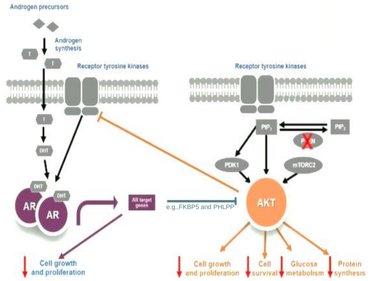
BACKGROUND

Androgen deprivation therapy (ADT) with or without antiandrogens such as enzalutamide is the mainstay of treatment in advanced prostate cancer (PC). However, new therapeutic strategies are needed for patients who relapse on antiandrogen therapy.

The glucocorticoid receptor (GR) has been implicated as a potential antiandrogen bypass mechanism. We have shown that GR antagonist ORIC-101 reverses GR-mediated resistance to enzalutamide in preclinical PC models (Zhou et al, AACR 2019).

Reciprocal crosstalk between AR and PI3K/AKT signaling pathway



De Bono JS et al, ESMO 2020

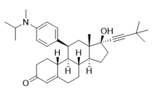
Activation of the PI3K/AKT pathway is a poor prognostic factor and another potential resistance mechanism to antiandrogen therapy. AKT inhibitors in combination with ADT or antiandrogens are in clinical development (e.g., NCT03072238, NCT04087174).

In this study, we tested preclinically whether activated GR confers resistance to the combination of enzalutamide with AKT inhibitors and whether co-treatment with ORIC-101 reverses GR-mediated resistance to AR/AKT blockade.

1. ORIC-101 GR Antagonist

ORIC-101 is a potent, selective, orally bioavailable small molecule GR antagonist with a favorable cytochrome P450 inhibition profile and lacking AR agonism, making this compound particularly suitable for combination with antiandrogens such as enzalutamide.

ORIC-101 (Steroidal)	
GR antagonism	IC_{50} = 7.3 nM
AR agonism	IC_{50} > 5000 nM
PR antagonism	IC_{50} = 22 nM
CYP3A4	IC_{50} = 1.6 µM
CYP2C8/CYP2C9	IC_{50} > 10 µM

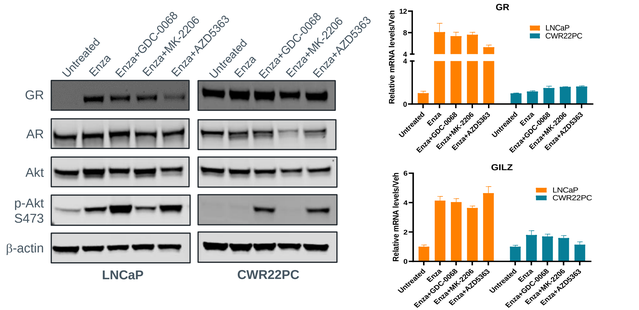


Rew et al, 2018

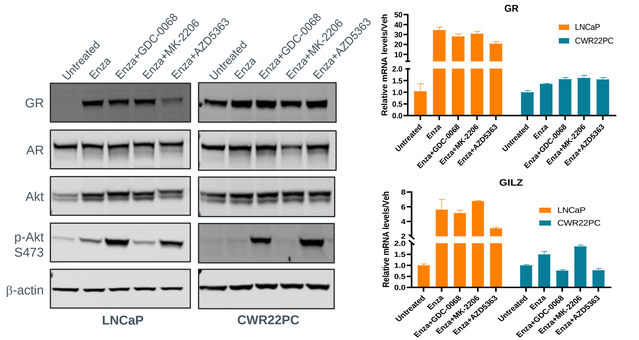
2. GR Activation is Induced by AR/AKT Blockade

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 cells and in PTEN-wildtype CWR22PC cells.

AR/AKT blockade activates GR in CSS media



AR/AKT blockade activates GR in full serum

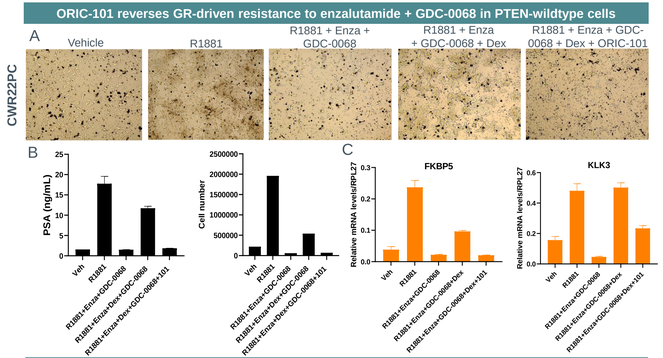


Upper panels, cells treated in phenol-red-free 10% CSS media for 7 days; **Lower panels**, cells treated in 10% FBS media for 7 days. Similar results were obtained with 30 nM dexamethasone supplementation, data not shown. Treatment: 2 µM enzalutamide (Enza), 100 nM GDC-0068, 100 nM MK-2206, 100 nM AZD5363

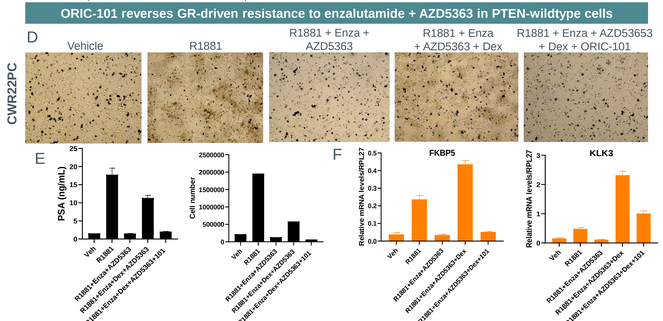
3. ORIC-101 Reverses GR-driven Resistance to AR/AKT Blockade in PTEN-wildtype CWR22PC Cells

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.

ORIC-101 reverses GR-driven resistance to enzalutamide + GDC-0068 in PTEN-wildtype cells



ORIC-101 reverses GR-driven resistance to enzalutamide + AZD5363 in PTEN-wildtype cells



Microscopy images (A,D) of 21-day proliferation assay in CWR22PC cells in CSS media with corresponding PSA levels (B,E) and GR target gene mRNA levels (C,F) measured at end point; media replenished every 7d. Treatment: 100 pM synthetic AR ligand R1881; 2 µM enzalutamide (Enza); 30 nM synthetic GR ligand dexamethasone (Dex); 0.5 µM ORIC-101 (101); 100 nM GDC-0068 or 100 nM AZD5363

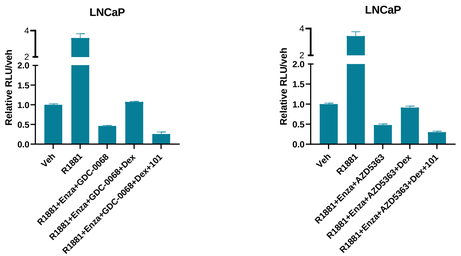
4. ORIC-101 Reverses GR-driven Resistance to AR/AKT Blockade in PTEN-null LNCaP Cells

The combination of AKT inhibitor GDC-0068 with abiraterone was found to significantly prolong radiographic progression-free survival over placebo with abiraterone, in a 1L mCRPC population with PTEN-loss (by IHC) (IPATential150 trial, De Bono JS et al, ESMO 2020).

We confirmed in PTEN-null LNCaP cells that GR activation partially restored cell viability allowing escape from AR/AKT blockade, which was completely reversed by ORIC-101.

ORIC-101 reverses GR-driven resistance to enzalutamide + GDC-0068 in PTEN-null cells

ORIC-101 reverses GR-driven resistance to enzalutamide + AZD5363 in PTEN-null cells



14-day Cell titer glo assay in LNCaP cells in CSS media. Treatment: 100 pM R1881; 2 µM enzalutamide (Enza); 30 nM dexamethasone (Dex); 0.5 µM ORIC-101 (101); 100 nM GDC-0068 or 100 nM AZD5363

CONCLUSIONS

- GR upregulation and activation drives resistance when antiandrogens 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 models

The combination of enzalutamide with GR antagonist ORIC-101 is being studied in patients with metastatic CRPC (Phase 1b, NCT04033328)