Prostate cancer is the second leading cause of cancer-related death in men. Androgen deprivation and blockade are commonly used to treat prostate cancer. However, relapse occurs with subsequent progression to metastatic castration-resistant prostate cancer (mCRPC).

The glucocorticoid receptor (GR) has been implicated as a potential antiandrogen bypass mechanism to enzalutamide treatment in prostate cancer (Arora et al., 2013; Isikbay et al., 2014). We have shown that the GR antagonist ORIC-101 completely restores enzalutamide sensitivity in preclinical CRPC models (Zhou et al., EORTC-NCI-AACR 2019).

Androgen receptor (AR) degraders are being evaluated as a new therapeutic modality for prostate cancer. ARV-110 is an AR PROTAC™ protein degrader in early clinical development (Petrylak et al., ASCO 2020).

Hypothesis: GR is a mechanism of resistance to AR degraders, and a GR antagonist reverses GR-mediated resistance to AR degradation in mCRPC.

1. AR degraders

Because the structure of ARV-110 has not been disclosed, we used two exemplary AR degrader (ARD) compounds, ARD1 and ARD2. We confirmed that both compounds (a) degrade AR protein in a dose-dependent manner (72hrs), (b) inhibit AR target gene expression (24hrs), and (c) blunt cell growth in CRPC cell lines.

2. ORIC-101 GR antagonist

ORIC-101 is a potent, selective, orally bioavailable small molecule GR antagonist with a favorable cytochrome P450 inhibition profile and without AR agonism, making this compound particularly suitable for combination with antiandrogens such as enzalutamide.

3. AR degradation upregulates GR expression

GR protein and mRNA levels are significantly upregulated in a time-dependent manner upon chronic ARD treatment, in GR-negative LNCaP cells and in CWR22PC cells with moderate GR expression pre-treatment.

4. AR degradation enhances GR signaling

GR target gene expression is also increased with both compounds, indicative of activated GR signaling.

5. ORIC-101 reverses GR-driven resistance to AR degraders in prostate cancer cells

AR degrader treatment blunts androgen-induced cell growth and PSA secretion. GR activation with glucocorticoids partially restores cell growth and PSA secretion in the presence of ARD treatment. This resistance is completely reversed by ORIC-101.

6. ORIC-101 inhibits glucocorticoid-induced AR and GR target gene expression

Glucocorticoids stimulate and ORIC-101 fully inhibits androgen-regulated gene expression in the end-of-study CWR22PC cells.

CONCLUSIONS

- GR may be a mechanism of resistance to AR degraders.
- GR antagonist ORIC-101 overcomes GR-driven resistance to AR degradation in preclinical prostate cancer models.
- More broadly, targeting GR may help overcome resistance to various modalities of antiandrogen therapy.
- The combination of enzalutamide with GR antagonist ORIC-101 is being studied in patients with metastatic CRPC (phase 1b, NCT04033328).