ORIC-101 Overcomes Resistance to Diverse Chemotherapeutics Across Cancer Types

Haiving Zhou, Shrvani Barkund, Aleksandr Pankov, Ganapatil Hegde, Wayne Kong, Padmini Narayanan, Jessica D. Sun, Omar Kabbarah, Lori S. Friedman, Anneleen Daemen
ORIC Pharmaceuticals, South San Francisco, CA 94080

BACKGROUND

Glucocorticoids circulate throughout the body and mediate multiple physiological processes including metabolism, cell growth, inflammation, apoptosis and differentiation (Aszer et al., 2016).

Upon glucocorticoid binding, the glucocorticoid receptor (GR) translocates into the nucleus and regulates gene transcription.

Elevated GR expression and dysregulated cortisol levels are associated with poor prognosis, drug resistance, and metastasis (Pan et al., 2011; Tangen et al., 2017; Obradovic et al., 2019).

Our prior studies revealed that GR antagonist ORIC-101 enhanced taxane response in preclinical breast cancer models (Zhou et al., 2019).

This preclinical study demonstrates the ability of ORIC-101 to overcome GR-mediated resistance to diverse chemotherapeutics across cancer types.

Phase 1b studies of ORIC-101 in combination with nab-paclitaxel in patients with advanced or metastatic solid tumors (NCT03928314) and in combination with enzalutamide in patients with metastatic prostate cancer progressing on enzalutamide (NCT04033328) are ongoing.

1. ORIC-101

ORIC-101 is a potent, selective, orally bioavailable small molecule GR antagonist with a more favorable cytochrome P450 inhibition profile than other clinical compounds, making it particularly suitable for combination with taxanes.

2. Experimental overview

[Table showing the IC50 values for ORIC-101 and other compounds]

3. GR is widely expressed in cancer cell lines and human tumors

[Graphs showing GR protein levels in TNBC and NSCLC cell lines (WB, top panels) and representative human TNBC and NSCLC tumor tissues (IHC, bottom panels).]

4. ORIC-101 reverses GR-mediated antiapoptosis

[Graphs showing representative examples from 8-12 tested lines per indication. GR-mediated chemoprotection and ORIC-101 reversal was only observed in GR-positive lines.]

5. ORIC-101 reverses GR-driven tumor growth

[Graphs showing representative colony formation assays across lines and indications (top panels): Gem, 50 mg/kg QID×3 IP, PTX, 15 mg/kg QID×5, IP indicated by black arrows; mean ± SEM. Additional xenograft studies in PDAC models are shown on AACC 2020 Poster #4132.]

6. ORIC-101 reverses EMT-like phenotype in vitro and in vivo

[Graphs showing TNBC, NSCLC, and PDAC models are shown on AACC 2020 Poster #4123.]

7. ORIC-101 overcomes resistance to chemotherapy by blocking GR-regulated transcription

[Graph showing working model of GR in the absence (green) or presence (red) of ORIC-101 in response to glucocorticoids.]

CONCLUSIONS

GR is widely expressed in cancer cell lines and tumor tissues functioning as a common resistance mechanism.

ORIC-101 is a potent, selective, orally bioavailable GR antagonist that:
- overcomes GR-mediated antiapoptosis to chemotherapeutics in vitro in multiple cancer types
- reverses GR-driven tumor growth in vitro and in vivo across indications
- inhibits GR-regulated transcriptional pathways such as EMT, stemness, and antiapoptosis

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