ORIC-101 Overcomes Glucocorticoid Receptor-Mediated Chemoresistance in Pancreatic Cancer Models

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BACKGROUND
Chemotherapy remains the main treatment option for patients with advanced and metastatic pancreatic ductal adenocarcinomas (PDAC), the most common type of pancreatic cancer. Activation of glucocorticoid receptor (GR) signaling confers resistance to chemotherapy, which contributes to dismal prognosis and poor survival rate. This preclinical study aims to investigate ORIC-101’s ability to overcome chemoresistance in pancreatic cancer models.

A phase 1b study of ORIC-101 in combination with nab-paclitaxel in patients with advanced or metastatic solid tumors is ongoing (NCT03928314).

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.

ORIC-101 (Steroidal)
- GR antagonism IC50 = 7.3 nM
- AR agonism IC50 > 5000 nM
- PR antagonism IC50 = 22 nM
- CYP2A4 IC50 = 1.6 µM
- CYP2C8/CYP2C9 IC50 > 10 µM

Rew et al., 2018

2. GR is widely expressed in PDAC models

3. ORIC-101 reverses GR-driven growth and potentiates chemotherapy

PDAC cell lines
- BxPC3
- SW1990

Growth Inhibition
- Days post treatment
- Tumor Growth Inhibition (TGI): vs. Cort + PTX
- PFS: Progression Free Survival, defined as tumor volume < 5000 mm³

Dex protects PDAC cells from chemotherapeutics in vitro, which is reversed by ORIC-101
ORIC-101 sensitizes PDAC xenografts to PTX

4. ORIC-101 blocks GR transcriptional activity

PDAC xenografts
- BxPC3
- HPAC
- SW1990

GR IHC (D6H2L)
- + ORIC-101
- #p<0.05, Log rank test

5. ORIC-101 inhibits GR-mediated pathways implicated in drug resistance

CONCLUSIONS
ORIC-101 is a potent, selective, orally bioavailable GR antagonist that:
- reverses GR-driven tumor growth and sensitizes PDAC models to chemotherapeutics, both in vitro and in vivo
- inhibits multiple GR-regulated pathways in drug resistance, such as EMT and hypoxia, in PDAC
- is in early clinical development: 1) in combination with nab-paclitaxel in patients with advanced or metastatic solid tumors (NCT03928314) and 2) in combination with enzalutamide in patients with metastatic prostate cancer progressing on enzalutamide (NCT04033328)

Please also visit:
- ORIC-101 comprehensively inhibits glucocorticoid pathways to overcome therapeutic resistance in pan-cancer models AACR 2020 Poster #4120
- ORIC-101 overcomes resistance to diverse chemotherapeutics across cancer types AACR 2020 Poster #4121