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 adenocarcinoma (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.

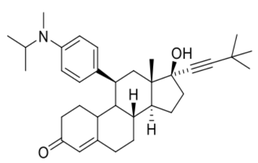
This preclinical study aims to investigate ORIC-101's ability to overcome chemoresistance in pancreatic cancer models.

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.

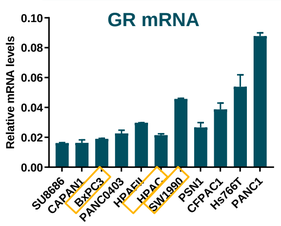
ORIC-101 (Steroidal)
GR antagonism IC_{50} = 7.3 nM
AR agonism IC_{50} > 5000 nM
PR antagonism IC_{50} = 22 nM
CYP3A4 IC_{50} = 1.6 µM
CYP2C8/CYP2C9 IC_{50} > 10 µM

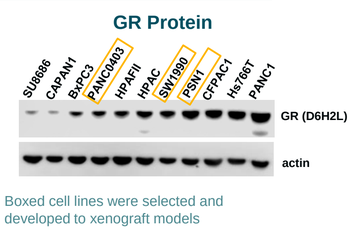


Rew et al., 2018

2. GR is widely expressed in PDAC models

PDAC cell lines

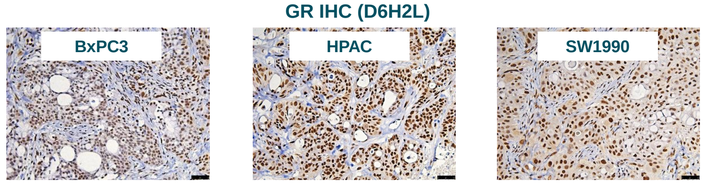




Boxed cell lines were selected and developed to xenograft models

PDAC xenografts

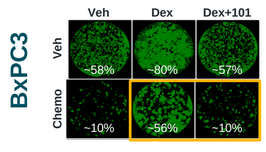
GR IHC (D6H2L)



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

PDAC cell lines

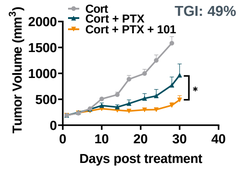
Colony Formation



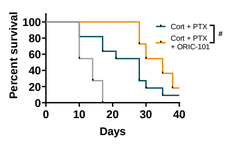
- Veh, vehicle
- Dex, dexamethasone
- Chemo: paclitaxel (PTX) + gemcitabine
- ORIC-101 (101), 150 mg/kg, QD x 21, PO
- PTX: 15 mg/kg, Q3D x 5, IP
- Cortisol (Cort), 100 mg/L in drinking water, ad lib

PDAC xenografts

Growth Inhibition



PFS



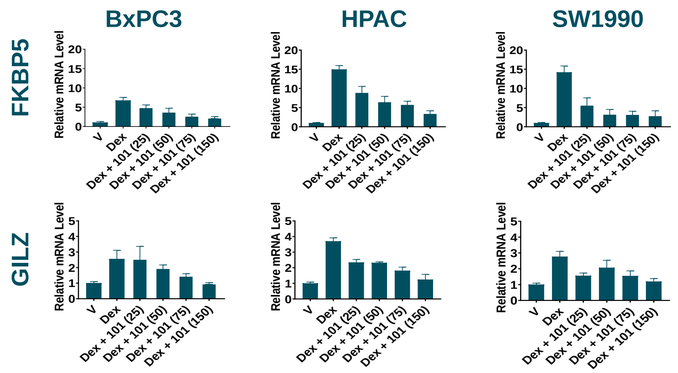
- Tumor growth inhibition (TGI): vs. Cort + PTX
- PFS: Progression Free Survival, defined as tumor volume < 500 mm^3
- Data are presented as mean ± SEM
- *p<0.05, t-test; #p<0.05, Log-rank test

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



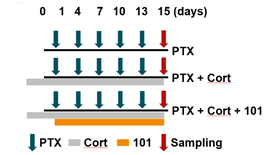
- 101: 25, 50, 75, and 150 mg/kg respectively, PO, once
- Dex: 0.5 mg/kg, IP, 30 mins post 101 administration
- Tumor sampling 6 hrs post 101 dosing
- Data are presented as mean ± SEM

ORIC-101 inhibits FKBP5 and GILZ in a dose-dependent manner in vivo

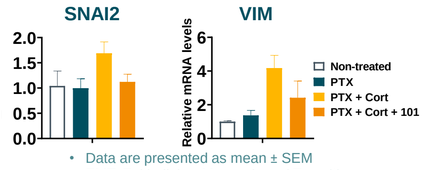
5. ORIC-101 inhibits GR-mediated pathways implicated in drug resistance

PDAC xenografts

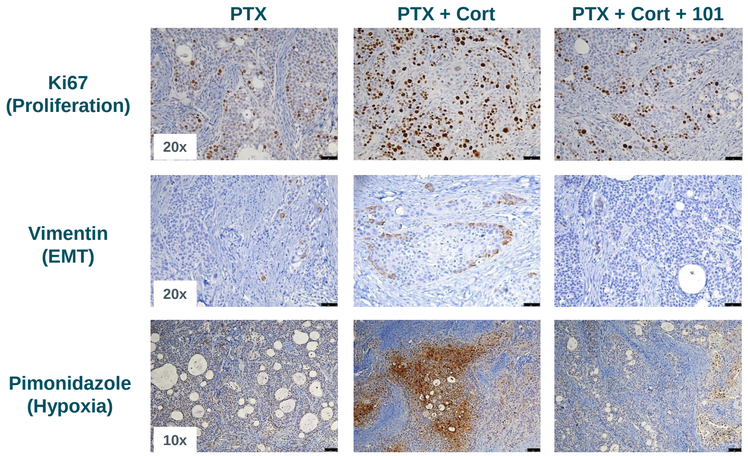
Dosing Scheme



PD Biomarkers



- Data are presented as mean ± SEM
- EMT: Epithelial-to-Mesenchymal Transition



ORIC-101 reverses GR-driven EMT-like phenotype

ORIC-101 attenuates hypoxia in tumor microenvironment

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

AACR Virtual Annual Meeting II, June 22-24, 2020, Poster#4123