

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.

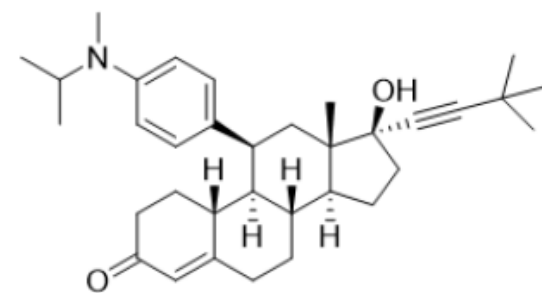
This preclinical study aims to investigate ORIC-101's ability to overcome chemoresistance in pancreatic cancer models.

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

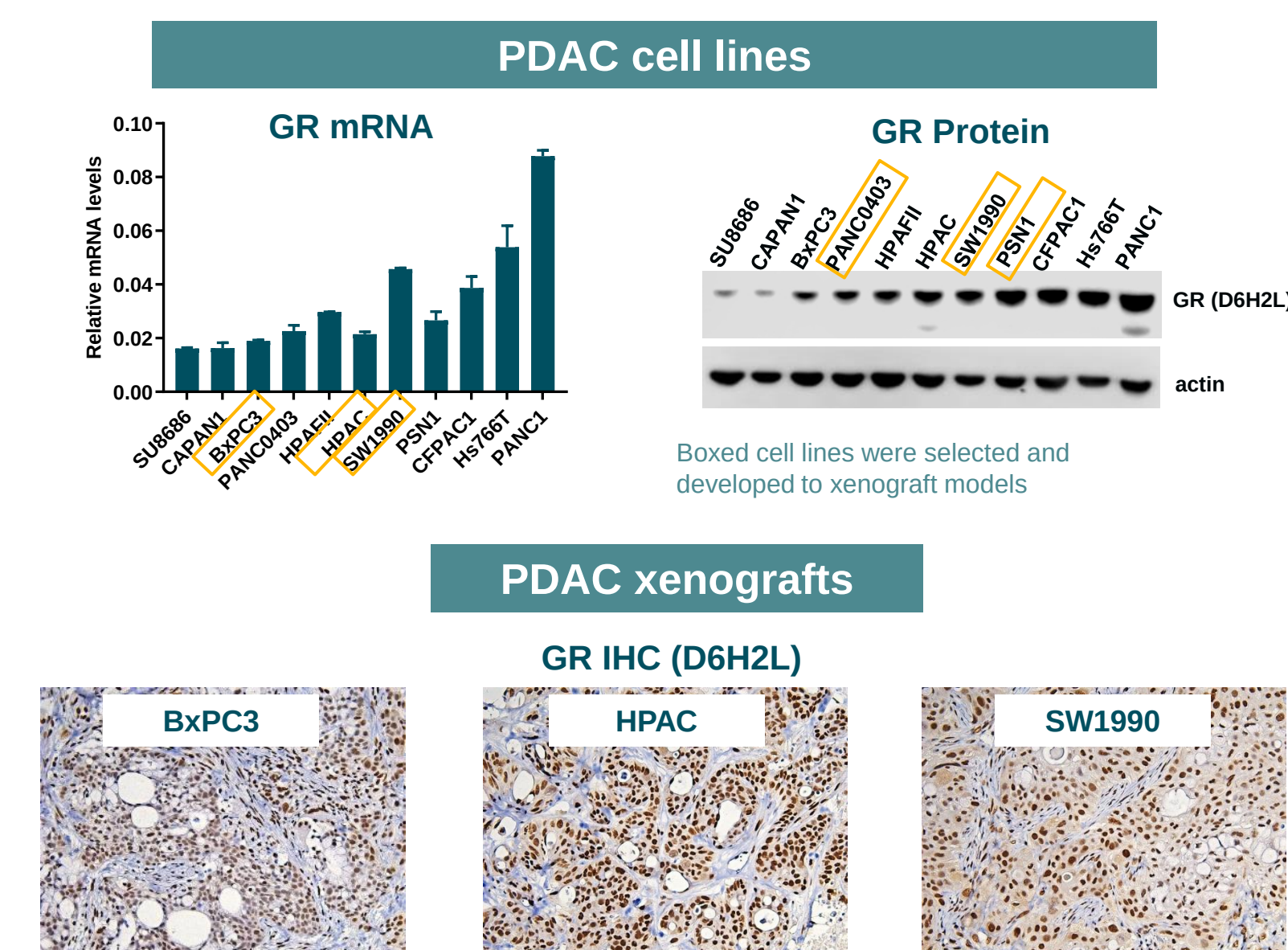
ORIC-101 is a potent, selective, orally bioavailable small molecule GR antagonist with a more favorable cytochrome P450 inhibition profile than other clinical compounds, making it particularly suitable for combination with taxanes.

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

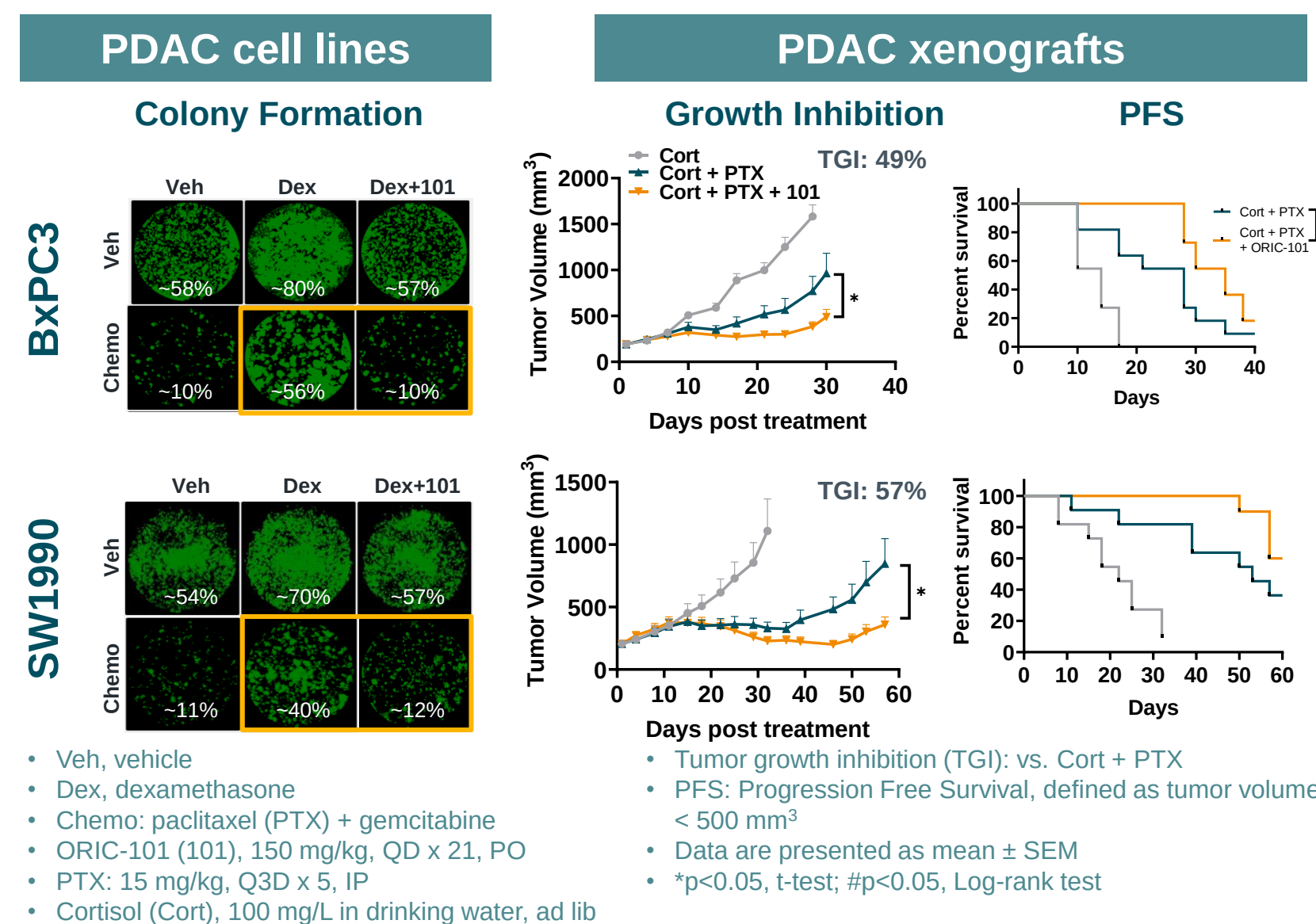


Rew et al., 2018

2. GR is widely expressed in PDAC models



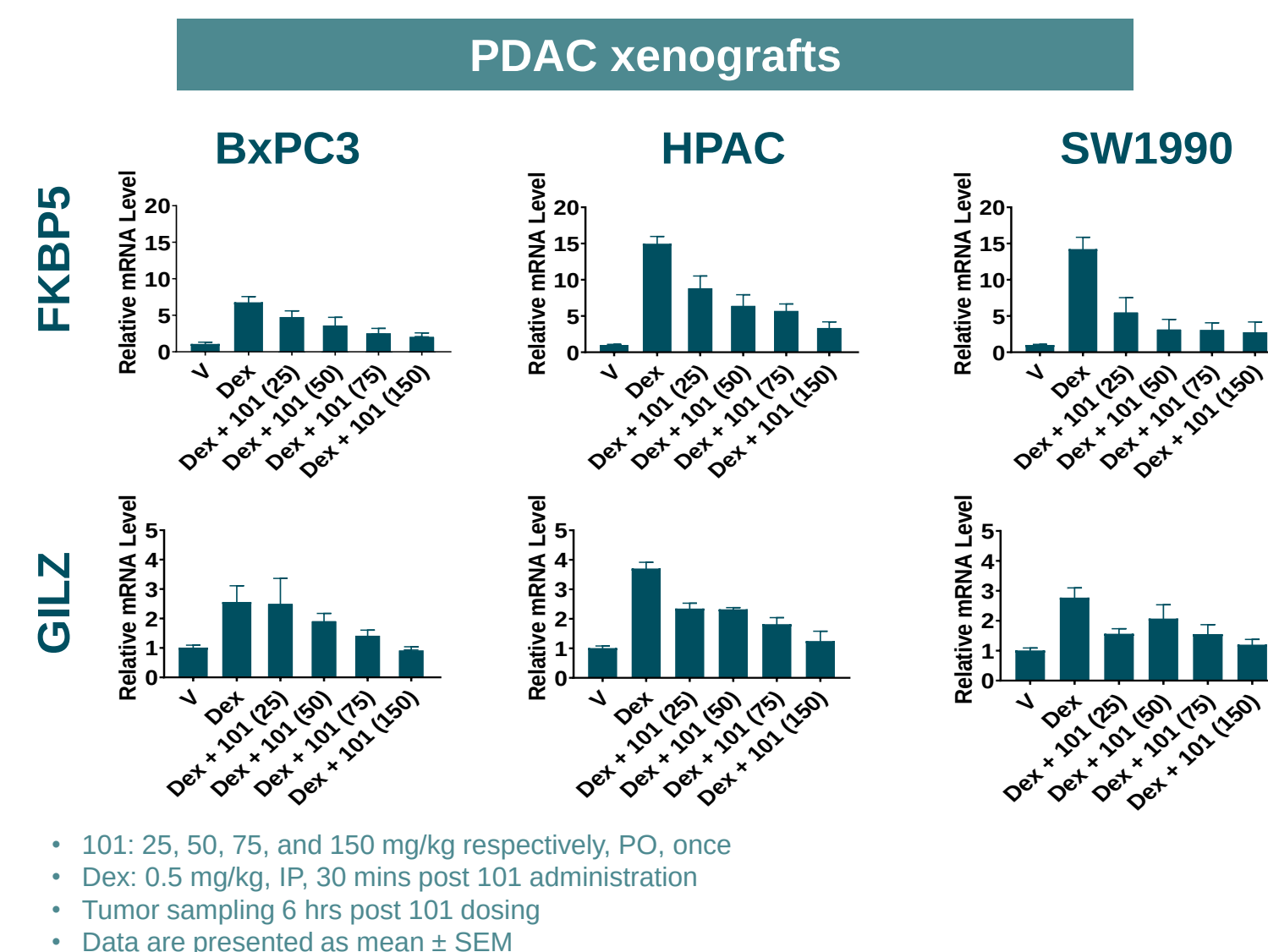
3. ORIC-101 reverses GR-driven growth and potentiates chemotherapy



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

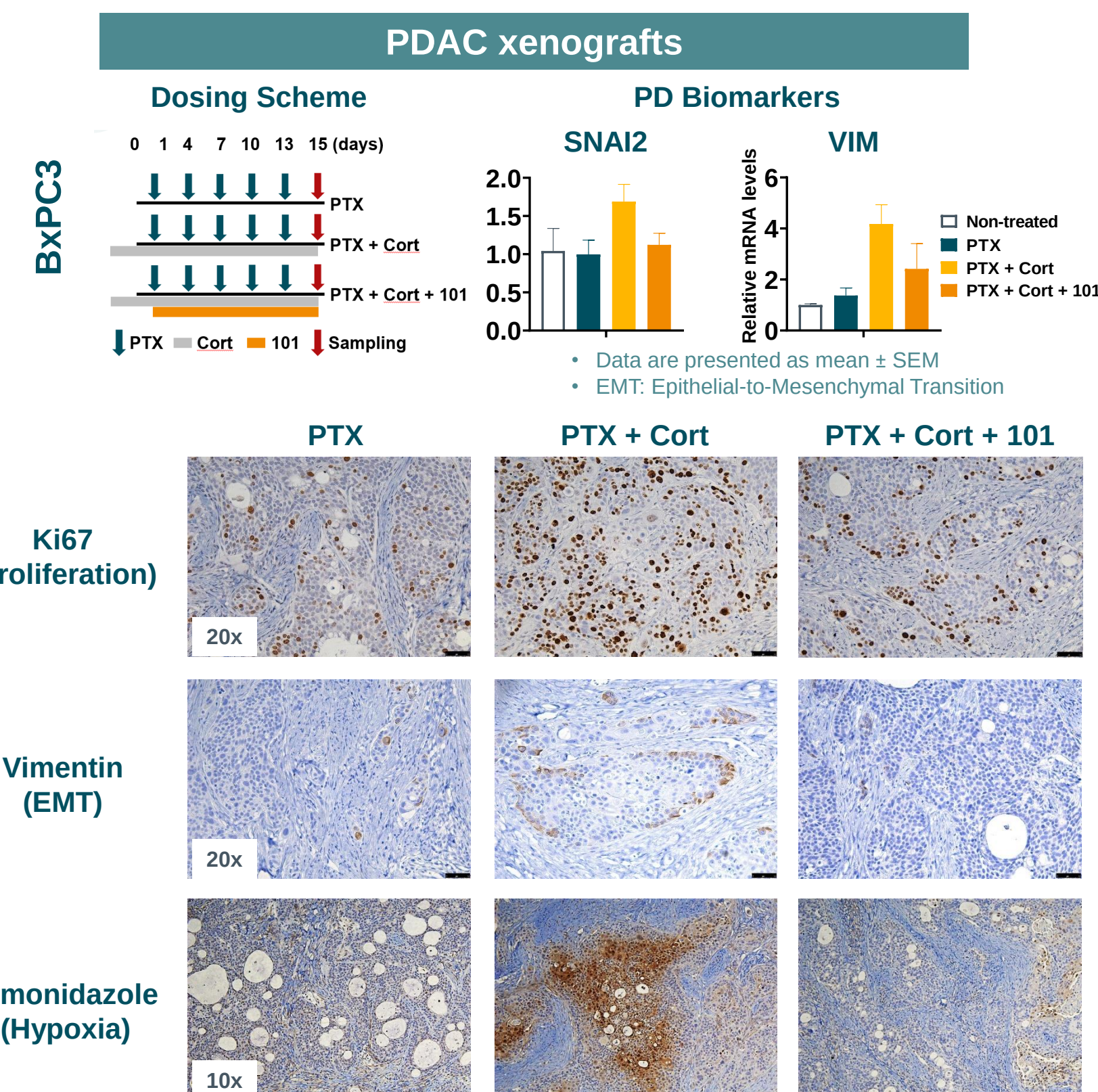
ORIC-101 sensitizes PDAC xenografts to PTX

4. ORIC-101 blocks GR transcriptional activity



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

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



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](#)