Enhancing endoplasmic reticulum stress for treating endocrine therapy resistant breast cancers driven by mutant estrogen receptors

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Introduction

Estrogen receptor alpha (ERα) mutations are common (30-40%) in metastatic endocrine therapy-resistant breast cancers (ETR-BC), enable resistance to endocrine therapies and are the molecular drivers of ETR-BC. We had previously shown that an oligobenzamide, ERX-41, could enhance endoplasmic reticulum stress (**ERS**) in ETR-BCs driven by mutant (MT) ERα, resulting in cancer cell death in vitro and in vivo. To enable clinical translation of ERX-41, we performed lead optimization, followed by preclinical and IND-enabling studies.

Methods and Materials

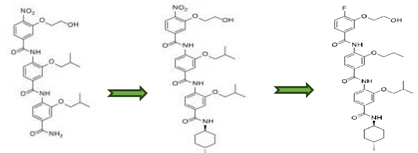
Over 2000 oligo-benzamides were designed, and tested in multiple BC models including those that express WT-ERα (MCF7, and ZR75) and BC models with acquired resistance (MCF7-TamR) and engineered models that express MT-ERα (MCF7-ERα-D538G, MCF7-ERα-Y537S, ZR75-ERα-D538G, ZR75-ERα-Y537S). Mechanistic validation studies were performed using RT-qPCR and Western blotting. Explants, organoids, cell line-(CDX) and patient-derived (PDX) xenografts were used to test the ex vivo and in vivo effectiveness of lead compound as a monotherapy and in combination with abemaciclib.

Conclusions

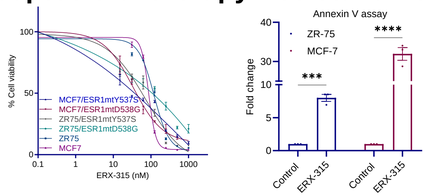
We identified a lead compound ERX-315, that represents a novel class of agents that cause catastrophic levels of ER stress, resulting in BC cell death, and that can successfully function against multiple forms of ETR-BC, including those driven by MT-ERα.

Results

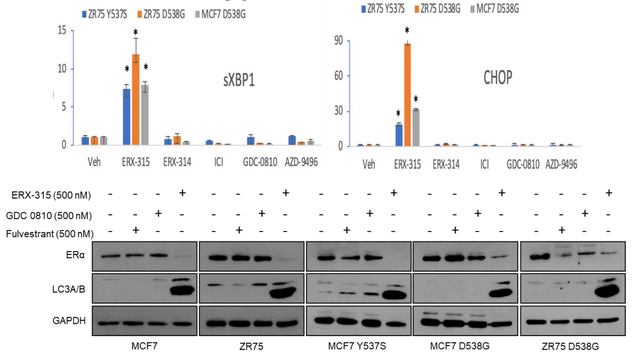
Derivation of ERX-315



ERX-315 reduces the cell viability and induces apoptosis of therapy resistant BC cells

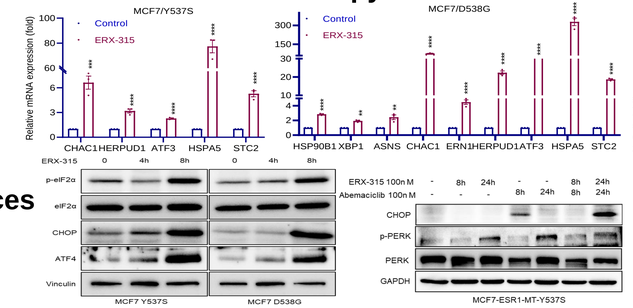


ERX-315 induces ERS in therapy sensitive and therapy resistant BC cells

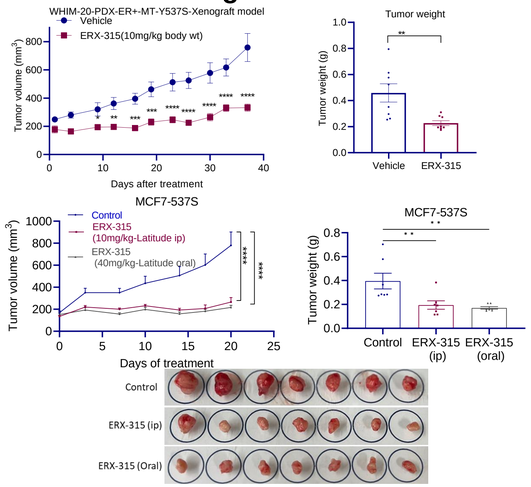


Results

ERX-315, alone or in combination with abemaciclib enhances ERS in therapy resistant BC cells

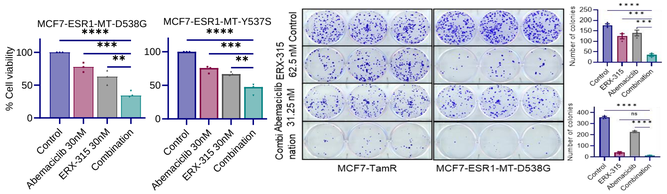


ERX-315 reduces the growth of therapy resistant BC xenograft tumors

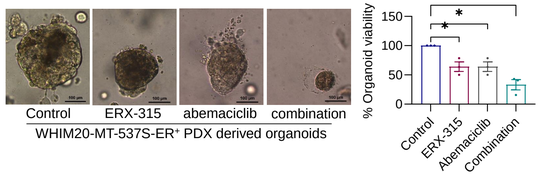


Results

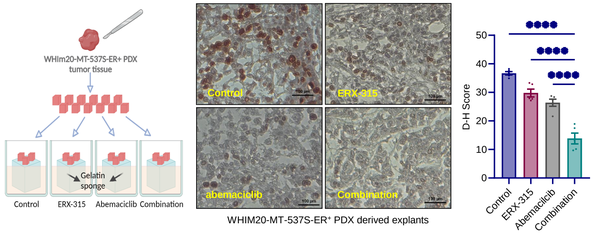
ERX-315+abemaciclib combination synergistically reduces the cell viability and clonogenicity of therapy resistant BC cells



ERX-315+abemaciclib combination therapy synergistically decreases the growth of organoids



ERX-315 in combination with abemaciclib synergistically decreases the proliferation of therapy resistant BC explants



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