Quantitative Regression of Estrogen Receptor Alpha Positive Breast Cancer

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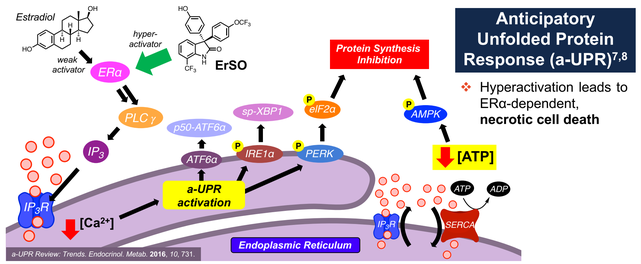
Introduction

- Current endocrine therapy (i.e. AI, SERMs, and SERDs) are slow acting, cytostatic, and lead to resistant disease (e.g. ERα Y537S or D538G).[1-6]
- **ErSO** is an orally bioavailable, first-in-class therapy for the treatment of resistant ERα+ breast cancer, with a planned IND submission 2020 Q3.
- **ErSO** triggers an immunogenic necrotic cell death via a novel hyperactivation of the anticipatory Unfolding Protein Response (a-UPR) without ERα degradation.

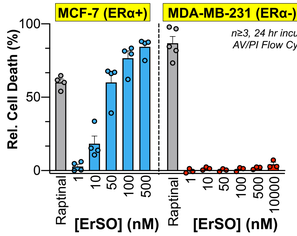
Novel Mechanism for Leveraging ERα Overexpression



Anticipatory Unfolded Protein Response (a-UPR)[7,8]

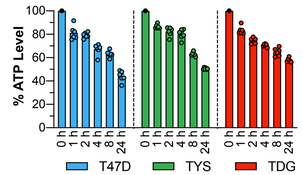
- Hyperactivation leads to ERα-dependent, **necrotic cell death**

ErSO: Cytotoxic a-UPR Activator



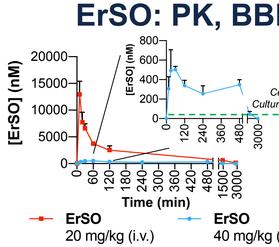
TYS: T47D with ERα^{Y537S}
TDG: T47D with ERα^{D538G}
MYS: MCF-7 with ERα^{Y537S}
MDG: MCF-7 with ERα^{D538G}

Cell Line	IC_{50} (nM)
T47D	16.4 (± 3.6)
TYS	11.1 (± 0.7)
TDG	16.6 (± 1.2)
MCF-7	15.1 (± 1.7)
MCF-7 par.	13.6 (± 0.2)
MYS	17.4 (± 0.3)
MDG	16.3 (± 0.2)
BT-474	22.9 (± 0.4)
ZR-75-1	42.8 (± 6.7)



n≥3, 24 hr incubation, Alamar Blue Fluorescence

ErSO: PK, BBB, and Tolerability

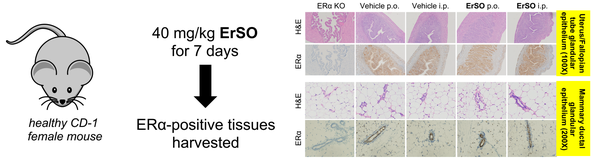


ErSO 20 mg/kg i.v.		
Parameter	Units	Estimate
AUC	min*ng/mL	411548.4
C_{max}	ng/mL	11956.7
$T_{1/2}$	min	69.3
C_{max}	μM	26.39

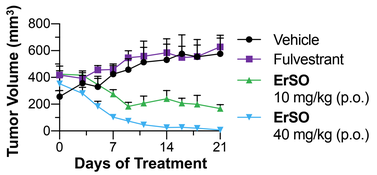
ErSO 40 mg/kg p.o.		
Parameter	Units	Estimate
AUC	min*ng/mL	137077.3
C_{max}	ng/mL	197.104
$T_{1/2}$	min	448
C_{max}	μM	0.435

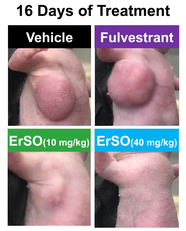
ErSO BBB Penetration
Brain:Blood Ratio = **27**:**73**
(I.V. administration)

No Effect on ERα+ Normal Tissues



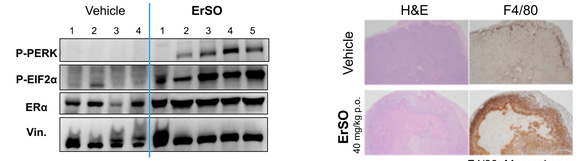
ErSO Treatment Leads to Complete Regression of Established Tumors





MCF-7 (ERα WT) orthotopic model, ovariectomized Nu/J mice with E2 pellet (0.36 mg), **ErSO** dosed daily (p.o.), Fulvestrant (5 mg/mouse) once-a-week, n = 6

a-UPR Activation in vivo → Immunogenic Necrosis

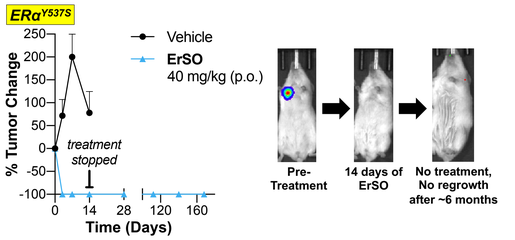


MCF-7 (ERα WT) bilateral orthotopic model, ovariectomized Nu/J mice with E2 pellet (0.36 mg), **ErSO** dosed daily (7 days, 40 mg/kg. p.o.), n = 4-5

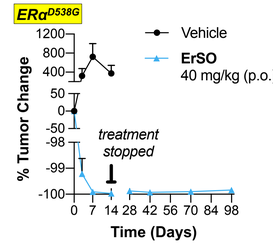
F4/80: Macrophages

ErSO Eradicates Mutant ERα Tumors with No Regrowth

Quantitative Regression of Mutant ERα Tumors



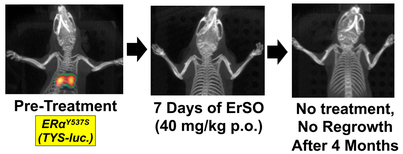
TYS-luc. orthotopic model, ovariectomized NSG mice no E2 pellet, **ErSO** dosed daily, n = 5-6



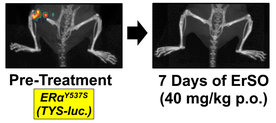
TDG-luc. orthotopic model, ovariectomized NSG mice no E2 pellet, **ErSO** dosed daily, n = 5-6

Quantitative Regression of Mutant ERα Metastasis

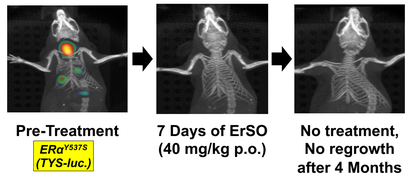
Lung Metastases



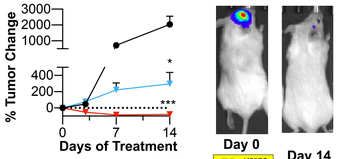
Bone Metastases



Multiple Metastases

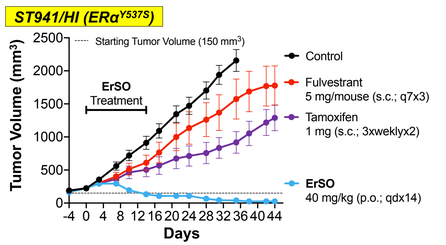


Brain Metastases

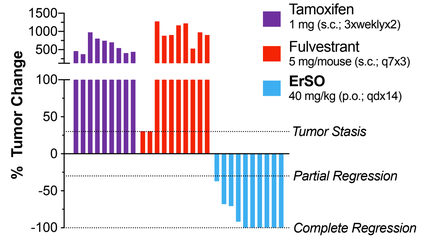


MYS-luc. Intracranial Model in NSG mice with no E2 pellet, **ErSO** dosed daily, n=4-5, *: p ≤ 0.05, ***: p ≤ 0.001

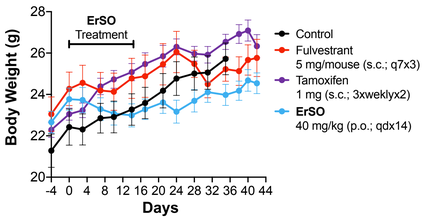
Regression of Mutant ERα PDX (Y537S)



Waterfall Plot 30 days post-dosing (d44)



No observed weight loss with ErSO dosing



Acknowledgments

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