OP-1250, a Complete Estrogen Receptor ANtagonist (CERAN) that penetrates the brain and prevents lethality from intracranial xenograft tumors expressing mutant ESR1

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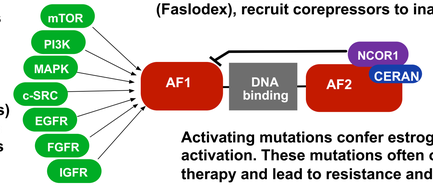
BACKGROUND: CERANs completely antagonize the Estrogen Receptor (ER)

Pro-proliferative signaling pathways activate ERα independent of estrogen via AF1. Selective ER Modulators (SERMs) are partial agonists unable to block this activation.



Complete ER Antagonists (CERANs), such as fulvestrant (Faslodex), recruit corepressors to inactivate AF1

Activating mutations confer estrogen-independent activation. These mutations often occur with endocrine therapy and lead to resistance and disease progression.

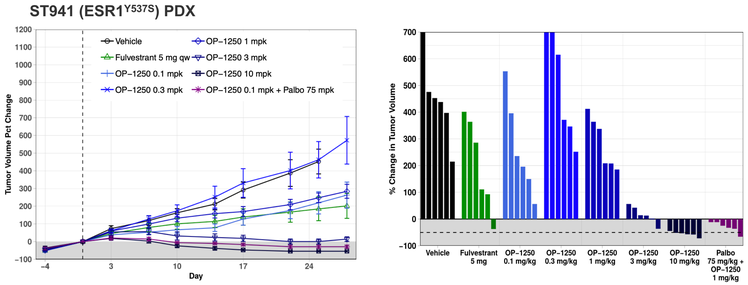
OP-1250 is a novel orally bioavailable CERAN with promising preclinical features;

- Completely inactivates wild type and mutant ERα by inhibiting both AF1 and AF2
- Completely blocks estrogen-driven proliferation in all ER+ breast cancer cell lines tested
- Robustly degrades ERα in all cell lines tested
- Exhibits a PK profile optimal for daily oral dosing and exhibits low toxicity
- Shrinks tumors in multiple tamoxifen-resistant xenograft and endocrine-resistant mutant ESR1 PDX models

Here we investigate the ability of OP-1250 to penetrate the brain and shrink tumors in an ER+ brain metastasis xenograft model.

References: 1) *Hodges-Gallagher, et al., Nature Comm., Jun 2018, Vol. 9:2268. 2) Shang and Brown, Science, 29 Mar 2002: Vol. 295, Issue 5564, pp. 2465-2468. 3) Webb, Nguyen, and Kushner, JBC, Vol. 278, 28 Feb 2003, pp. 6912–6920. 4) Toy, et al., Nat. Genet. 2013, Vol. 45, pp. 1439-1445. 5) Jeselsohn, et al., Clin. Cancer Res. 2014, Vol. 20, pp.1757-1767. 6) Hodges-Gallagher, et al., poster SABCS 2019.*

OP-1250 shrinks breast tumors expressing mutant ESR1^{Y537S} at 3-10 mg/kg



28-day study of OP-1250 treatment in the ST941 PDX model. These tumors contain ESR1^{Y537S} mutation and grow without E2 supplementation and is resistant to endocrine therapies. Tumors were implanted in nude mice (n=6) and measured twice weekly. OP-1250 and palbociclib were orally administered QD, while fulvestrant (Faslodex) was dosed QW (SC). In vivo experiments were performed by START in San Antonio, TX.

OP-1250 shrinks mutant ESR1 tumors in the brain and prevents lethality in an intracranial model of metastasis

ST941 PDX cells (ESR1-Y537S) resected from serially grown intracranial tumors

250k single cells implanted intracranially with stereo device

Jackson nude mice (ovaries intact)

+E2 in drinking water

2-3 weeks

MRI to confirm tumor growth (remove E2)

-3 days

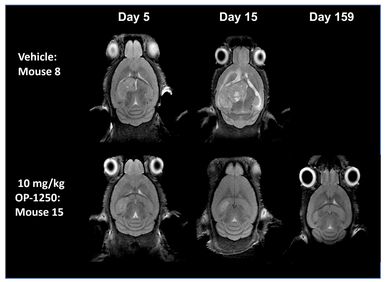
Begin dosing

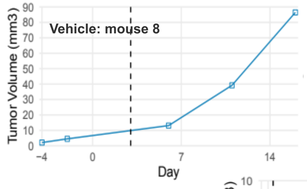
0

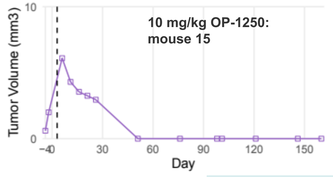
minerva IMAGING

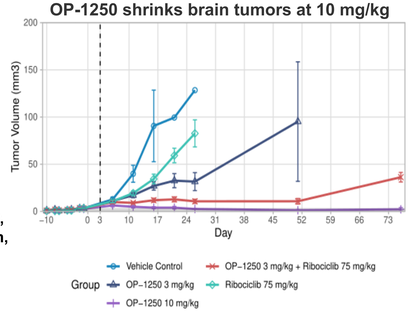
Arms:
Vehicle
OP-1250 3 mg/kg
OP-1250 10 mg/kg
Ribociclib 75 mg/kg
OP-1250 3 mg/kg + ribo 75 mg/kg

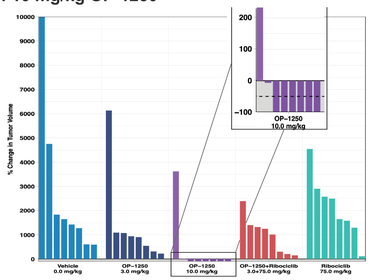
Endpoints: tumor volume, survival
Criterion of termination based on weight, appearance and behavior (self-mutilation, seizures, unresponsiveness, etc.)



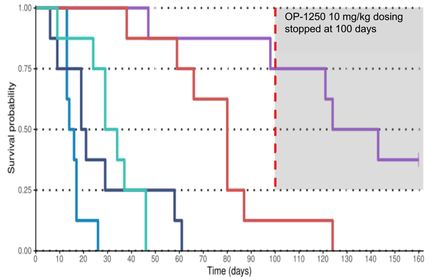






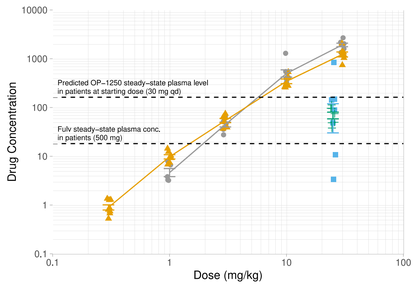


10 mg/kg OP-1250 prolongs survival in ER+ brain metastasis model



Of the 3 surviving mice at end of study, two had no detectable tumor, and one had a slow growing tumor

OP-1250 robustly penetrates brain



Treatment	Dose (mg/kg)	Brain (mg/g)	Plasma (mg/kg)	Brain-to-plasma Ratio
OP-1250	1	4.629	10.488	0.441
OP-1250	3	44.718	54.111	0.826
OP-1250	**10**	**498.68**	**344.263**	**1.449**
OP-1250	30	1919.52	1225.744	1.566
Fulvestrant	50/25	60.103	68.594	0.876

Penetration of OP-1250 in brain. Shown are concentrations of OP-1250 and Fulvestrant in plasma and brain at end of 28-day xenograft study in ovariectomized nude mice. OP-1250 was administered orally qd, while fulvestrant was injected s.c. at 25 mg/kg qw with a 50 mg/kg loading dose administered the first week.

Key Findings and Clinical Implications

- OP-1250 is a potent CERAN (Complete ER-antagonist) of both wild type and mutant ERα.
- OP-1250 shrinks breast tumors expressing mutant ERα in a PDX model of endocrine resistance.
- OP-1250 penetrates the rodent brain, with 1.5 times more OP-1250 in brain than plasma.
- OP-1250 shrinks tumors in an intracranial xenograft model of brain metastasis.
- OP-1250 prevents lethality from brain metastasis

The observed preclinical safety profile and efficacy data clearly support the clinical development of OP-1250. A phase 1 dose escalation and expansion study of OP-1250 in previously treated patients with ER+ metastatic breast cancer will be initiated in 2020 and will include an exploratory cohort of CNS patients.