The complete estrogen receptor antagonist (CERAN) OP-1250 shrinks ER+ breast cancer tumors expressing the ESR1-Y537S mutant estrogen receptor in an intracranial xenograft model of brain metastases

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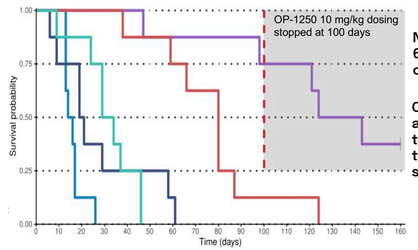
OP-1250 is a Complete Estrogen Receptor Antagonist (CERAN) and Selective Estrogen Receptor Degrader (SERD) that robustly shrinks wild-type and mutant ER+ breast tumors in preclinical xenograft models

OP-1250 is a small molecule drug candidate with many promising features for the treatment of ER+ breast cancer:

- Completely inactivates wild type and constitutively active variants of ERα by inhibiting both AF1 and AF2[1]
- Degrades ERα and completely blocks estrogen-driven proliferation in all ER+ breast cancer cell lines tested[1]
- Shrinks tumors in multiple endocrine resistant xenograft and mutant ESR1-Y537S PDX models[1]
- Well tolerated in animal studies
- Exhibits a PK profile optimal for daily oral dosing[2]
- OP-1250 is currently in a phase I/II trial for recurrent, locally advanced or metastatic ER+/HER2- breast cancer
- We recently reported that OP-1250 penetrates the rodent brain, with up to 1.5 times more OP-1250 measured in the brain than in plasma[3]

Rationale for investigating OP-1250 to treat ERα breast cancer brain metastases:

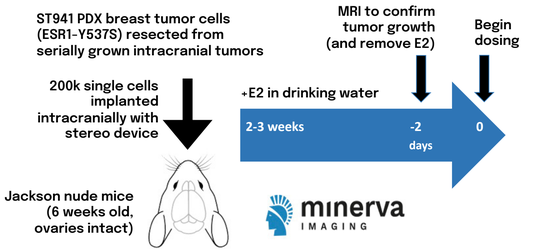
- Although clear clinical evidence is lacking for treating patients with endocrine therapy several anecdotal reports indicate tamoxifen is efficacious in some patients[4–7]
- Tamoxifen and its metabolites have been detected in human brain tissue at levels up to 46-fold higher than those measure in serum[8]
- In a recent previous study 10 mg/kg OP-1250 robustly shrunk tumors expressing mutant ERα in an intracranial breast cancer model[3]
- Here we compare the efficacy of OP-1250 versus Tamoxifen, Fulvestrant and ovariectomy to shrink tumors in an intracranial xenograft tumor model



No detectable tumors in 6/8 animals after 80 days of 10 mg/kg OP-1250

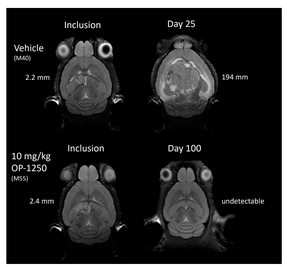
Of the 3 surviving mice at the end of the study, two had no detectable tumor, and one had a slow growing tumor

Intracranial patient derived xenograft (PDX) tumor model with breast cancer cells expressing mutant ESR1-Y537S receptors



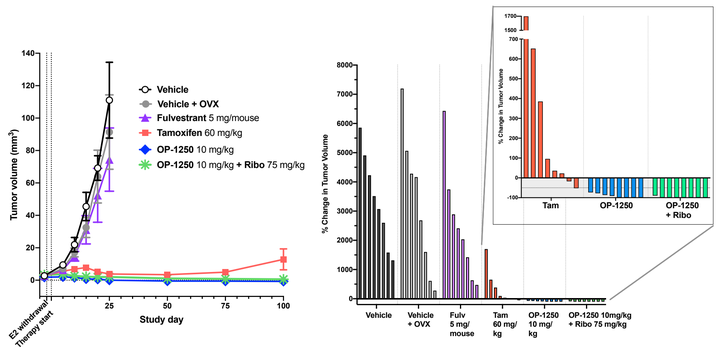
Arms:
Vehicle
Vehicle with ovariectomy
Fulvestrant 5 mg/mouse (SC, QW)
Tamoxifen 60 mg/kg (PO, QD)
OP-1250 10 mg/kg (PO, QD)
OP-1250 10 mg/kg + ribociclib 75 mg/kg (PO, QD)

Endpoints: tumor volume, RECIST-like response evaluation, survival
Criterion of termination: more than 10% loss of body weight, appearance and behavior (self-mutilation, seizures, unresponsiveness, etc.)

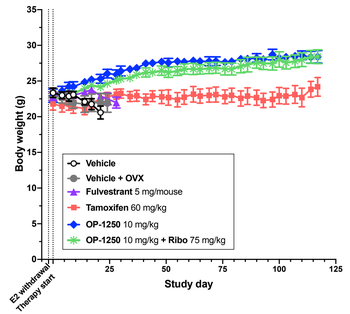


10 mg/kg OP-1250 is superior to tamoxifen, fulvestrant and ovariectomy in shrinking mutant ESR1-Y537S tumors in an intracranial model of ER+ breast cancer brain metastasis

After 100 days tumors in mice treated with OP-1250 remain small or undetectable while tumors in mice treated with tamoxifen have started to grow



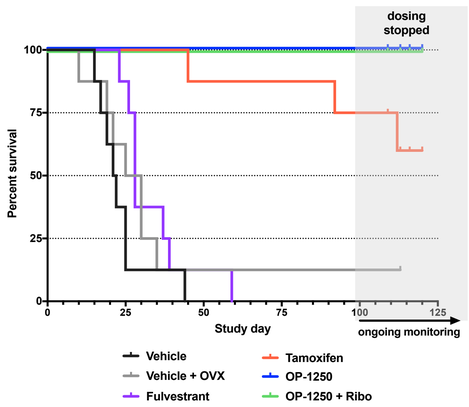
Animals treated with OP-1250 gain weight as expected for juvenile mice



Treatment	Endpoint	n
Vehicle PO, QD	PD	8
	SD	0
	PR	0
	CR	0
Vehicle + OVX PO, QD	PD	7
	SD	1
	PR	0
	CR	0
5 mg Fulvestrant SC, QW	PD	8
	SD	0
	PR	0
	CR	0
60 mg/kg Tamoxifen PO, QD	PD	6
	SD	1
	PR	1
	CR	0
10 mg/kg OP-1250 PO, QD	PD	0
	SD	0
	PR	4
	CR	4
10 mg/kg OP-1250 + 75 mg/kg Ribociclib PO, QD	PD	0
	SD	0
	PR	1
	CR	7

Endpoint criteria: PD (progressed disease) >20% increase in tumor size; PR (partial response) >30% decrease in tumor size; CR (complete response): no tumor observed; SD (stable disease): does not meet above criteria.

All animals treated with 10 mg/kg OP-1250 (+/- Ribociclib) survived past 120 days



Key findings and clinical significance

- Here we report that OP-1250 shrinks tumors in a preclinical intracranial xenograft metastatic tumor model expressing mutant estrogen receptor ESR1-Y537S. All tumors responded to OP-1250 treatment. 4/8 tumors treated with OP-1250 alone and 7/8 treated with OP-1250 + Ribociclib were undetectable after 100 days.
- OP-1250 treatment was superior in shrinking ER+ tumors in this model compared to other endocrine therapies tested, including ovariectomy, fulvestrant and tamoxifen.
- OP-1250 treatment does not interfere with the growth of juvenile mice in this model.
- OP-1250 prevented death in all animals at day 120 while the vast majority of untreated animals die by day 25.
- These data suggest that OP-1250 may be an active treatment for patients with brain metastasis from ER+ breast cancer and provide a strong rationale for clinical study in this area.
- OP-1250 is currently in a phase I/II dose escalation and expansion clinical trial in breast cancer patients with recurrent, locally advanced or metastatic ER+/HER2- tumors whose disease has progressed on prior endocrine therapy.

References: 1) Hodges-Gallagher, et al., poster SABCS 2019. 2) Hodges-Gallagher, et al., poster SABCS 2020. 3) Hodges-Gallagher, et al., poster AACR 2020. 4) Leone JP, Lin NU. Curr Oncol Rep. 2019 Apr 8;21(6):49. 5) Pors H, et al. J Neurooncol. 1991;10(2):173-177. 6) Salvati M, et al. Tumori. 1993;79(5):359-362. 7) Wang Q, et al. Onco Targets Ther. 2019;12:1389-1393. 8) Lien E. et al. Br J Cancer. 1991;63(4):641-645. doi:10.1038/bjc.1991.147.