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

- OP-1250 is an oral small molecule antagonist of the estrogen receptor that completely inactivates both activation function domains (AF1 and AF2) of both wild-type and mutant ERα, resulting in a complete block of ER-driven transcriptional and proliferative signaling in breast cancer cells.1
- OP-1250 robustly degrades ERα in multiple breast cancer cell lines.2
- OP-1250 shrinks tumors expressing both wild-type and mutant ERα in multiple ER-/HER2- preclinical xenograft models.3
- OP-1250 has robust CNS penetration and shrinks tumors in a preclinical brain metastasis model.1

While both OP-1250 and fulvestrant are complete ER antagonists, OP-1250 has demonstrated superior efficacy in shrinking tumors in multiple head-to-head preclinical xenograft studies. Here we investigate if this superiority is due to OP-1250’s favorable PK profile and its ability to reach, and accumulate within, tumor targets.

Background: OP-1250 Shrinks Tumors in an Estrogen-Independent Postmenopausal PDX Preclinical Breast Cancer Model

A clinically relevant dose of fulvestrant did not shrink tumors in this model while 3 mg/kg OP-1250 shrunk tumors more than 50%.

In contrast to fulvestrant, OP-1250 accumulates 45-fold in breast tumors in a preclinical xenograft model

Table 1. Pharmacokinetic parameters following administration of a single oral dose of OP-1250 administered to multiple species.

![Figure 1. Pharmacokinetic parameters following administration of a single oral dose of OP-1250 administered to multiple species.](image1)

**References**
1. Hodges-Gallagher et al., 2019 meeting poster #153
2. Hodges-Gallagher et al., 2019 meeting poster #153
3. Hodges-Gallagher et al., 2019 meeting poster #153

The superior efficacy observed by OP-1250 over fulvestrant in shrinking tumors in preclinical studies may be explained by its ability to accumulate within tumors

Conclusions and clinical significance of having both excellent PK/PD and complete antagonism of the ER

- OP-1250 is an orally bioavailable complete antagonist of the ER that shrinks breast tumors with as low as 3 mg/kg of daily dosing in a preclinical model of estrogen-independent breast cancer model that expresses the EBR Y537S mutation.
- The clinical efficacy of fulvestrant, which must be administered intramuscularly, is limited by its poor oral bioavailability and pharmacokinetics. Here we demonstrate that OP-1250 is superior to fulvestrant in shrinking tumors in xenograft models and this efficacy is correlated with the accumulation of OP-1250 within tumors.
- OP-1250 is orally bioavailable, and has a half-life in preclinical models that supports oral, once a day dosing in patients.
- OP-1250 is a promising new agent for ER- breast cancer. We have recently initiated a phase I dose escalation and expansion trial of OP-1250 in patients with recurrent, locally advanced or metastatic ER-/HER2- breast cancer whose disease has progressed on prior endocrine therapy.