The Complete Estrogen Receptor Antagonist OP-1250 Shrinks Tumors in Xenograft Models and Has Favorable Preclinical Pharmacokinetic Attributes

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Abstract #1410

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.[2]
- OP-1250 has robust CNS penetration and shrinks tumors in a preclinical brain metastasis model.[3]

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.

OP-1250 has dose proportional steady state exposure with minimal peak to trough variation in multiple species

Bioavailability and half-life of OP-1250 in multiple species

Species	Dose (mg/kg)	%F	T ½ (h)
Mouse	5	71.8	10.2
Rat	5	55%	16.1
Dog	10	88.9%	106
Monkey	10	44.4%	34.1

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

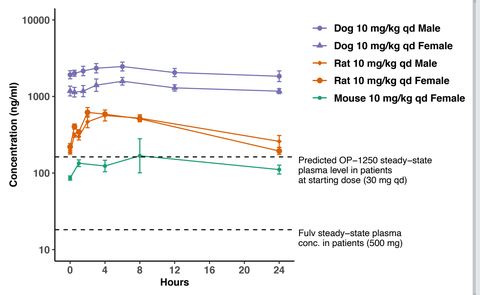
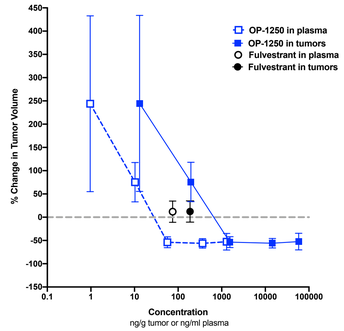


Figure 2. Serum concentrations of OP-1250 were measured after the final dose of 27-28 day multi-species studies with 10 mg/kg OP-1250, PO, QD.

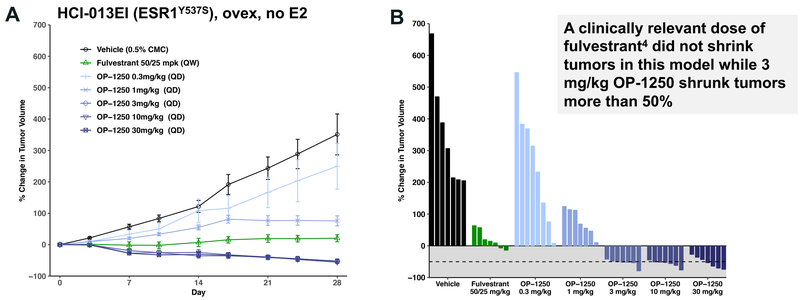
The superior efficacy observed by OP-1250 over fulvestrant in shrinking tumors in preclinical studies may be explained by its ability to accumulate within tumors



Tumor shrinkage by OP-1250 correlates with accumulation of OP-1250 in tumors in the preclinical HCI-013EI PDX model

Figure 4. Accumulation of OP-1250 in tumors and plasma relative to tumor shrinkage at end of 28-day study treating ovariectomized mice in the ESR1^{Y537S} estrogen-independent HCI-013EI PDX model. See figure 1 for treatment details.

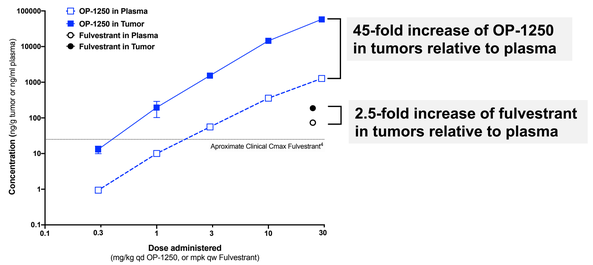
Background: OP-1250 shrinks tumors expressing mutant ER in an estrogen-independent postmenopausal PDX preclinical breast cancer model



A clinically relevant dose of fulvestrant[4] did not shrink tumors in this model while 3 mg/kg OP-1250 shrunk tumors more than 50%

Figure 1. 28-day study of OP-1250 treatment in the HCI-013EI patient derived xenograft (PDX) model, which contains ESR1^{Y537S} mutation, in ovariectomized (ovex) mice. HCI-013EI, a subline of HCI-013 tumors, grows in the absence of E2 supplementation. Note that fulvestrant was dosed weekly subcutaneously while OP-1250 was dosed PO. Figure was previously presented at the 2019 SABCS meeting[1].

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



45-fold increase of OP-1250 in tumors relative to plasma

2.5-fold increase of fulvestrant in tumors relative to plasma

Figure 3. Accumulation of OP-1250 in tumors and plasma relative to dose at end of 28-day study treating mice in the ESR1^{Y537S} estrogen-independent HCI-013E1 PDX model. See figure 1 for treatment details.

References
1) Hodges-Gallagher et al., EORTC/NCI/AACR , 2020 meeting poster #193
2) Hodges-Gallagher et al., SABCS, 2019 meeting poster #PS-05-02.
3) Hodges-Gallagher et al. AACR, 2020 meeting poster #4376.
4) Wardell, et al. Breast Cancer Research and Treatment volume 179, pages 67–77(2020)

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 ESR1^{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/II 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.