Development of OP-1250, an Oral Complete Estrogen Receptor ANtagonist (CERAN) that Shrinks ER-positive Breast Tumors in Xenograft Models

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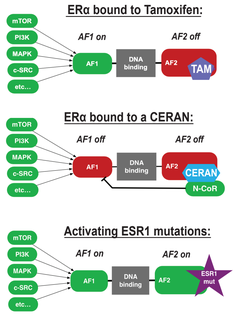
Introduction

Partial ERα agonists, such as tamoxifen, block activation function 2 (AF2) but allow activation of activation function 1 (AF1) and cooperate with other signaling pathways to drive cell proliferation and breast cancer progression.

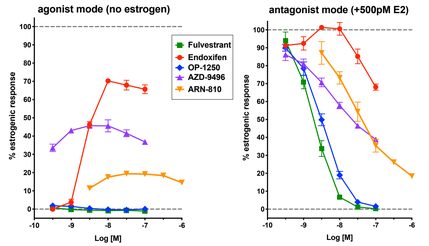
Complete ERα Antagonists (CERANs), such as fulvestrant, recruit corepressors to the ERα complex and lead to inactivation of both AF1 and AF2. Whereas CERANs are selective estrogen receptor degraders (SERDs), some SERDs have agonist activity on AF1.

During treatment with aromatase inhibitors for ER+ metastatic breast cancer, mutations arise in ESR1, the gene that encodes ERα, and confer AF2 activity in the absence of estrogen. We here explore whether the mutations confer AF1 activity and if so whether the novel CERAN OP-1250 can counter this activity.

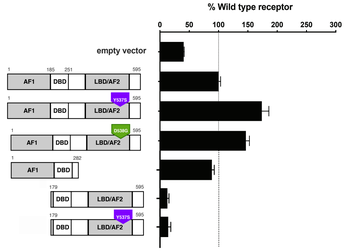


OP-1250 is a complete ER-antagonist (CERAN) that blocks AF1 and AF2 of both wild type and mutant ERα

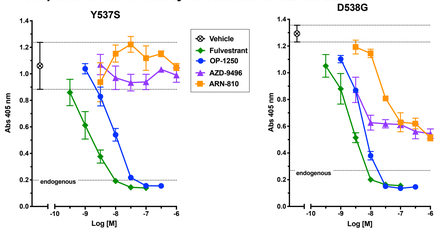
A OP-1250 action on the AF1- responsive alkaline phosphatase (AP) gene in cultured uterine cells



B AF1 of transfected ERα is required for induction of AP activity



C OP-1250 inhibits AF-1 of the transfected Y537S, D538G mutant receptors in the AP assay in contrast to SERM/SERDS



D OP-1250 action on the increase in uterine weight of ovex mice

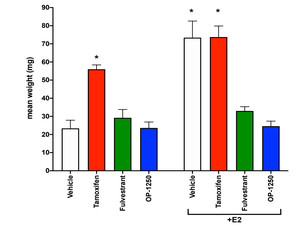


Figure 1. Alkaline phosphatase (AP) activity was assayed by treating Ishikawa endometrial cells with ligands in E2-depleted media for 3 days. Absorbance was read after incubation with chromogenic substrate. In panels B and C cells were also transfected with indicated ER constructs. Unless indicated, cells were treated in the absence of E2. D) Uterine wet weight was measured in ovariectomized BALB/c mice (n = 5) treated QD x 3 with 100 mg/kg OP-1250, 50 mg/kg tamoxifen, 50 µl fulvestrant (Faslodex, (SC)) and/or 0.1 µg estradiol (E2, (SC)). * p ≤ 0.05 relative to vehicle.

OP-1250 fully blocks estrogen-driven proliferation of ER+ breast cancer cells

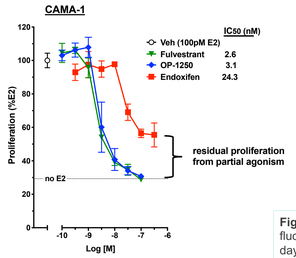


Table 1. SERM/SERDs do not completely antagonize E2-stimulated proliferation in CAMA-1 breast cancer cells

Ligand	Mean % residual proliferation
Endoxifen	32
ARN-810	13
RAD1901	14
AZD-9496	7
OP-1250	2
Fulvestrant	-2

Figure 2 and Table 1. Cell proliferation in CAMA-1 cells was determined by measuring fluorescence of a DNA-binding dye after treating with ligands in E2-depleted media for 7-9 days. Residual proliferation determined by normalizing data to +E2 (100%) and -E2 (0%).

OP-1250 is a pure antagonist across the full spectrum of E2 regulated genes

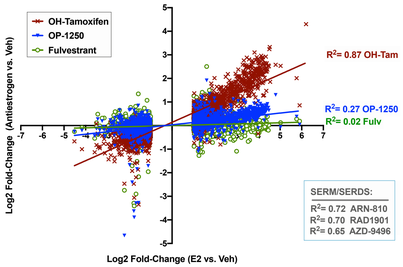


Figure 3. RNA-seq analysis was performed on CAMA-1 cells treated with 316 nM antiestrogen, or 100 pM E2 for 24 hours in E2-depleted media. Shown are expression of genes significantly regulated by E2 (log2 fold-change over vehicle ≥1, adj. p ≤ 0.05 (x-axis)). Higher R^2 indicates greater correlation of antiestrogen-mediated gene expression compared to E2.

OP-1250 degrades ERα in multiple cell lines

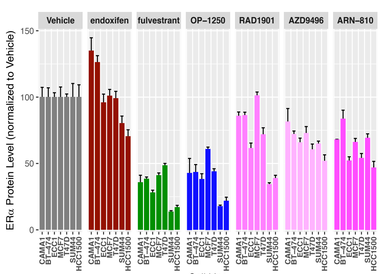
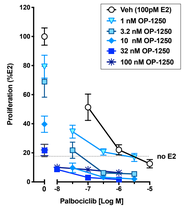


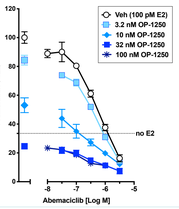
Figure 4. Cell lines were treated with 316 nM ligand in E2-depleted media for 4 hours. Lysates were immunoblotted with antibodies to ERα, normalized to vehicle (100%).

OP-1250 is effective in combination with CDK4/6 and PI3K inhibitors

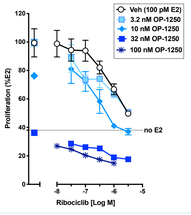
A OP-1250 plus Palbociclib



B OP-1250 plus Abemaciclib



C OP-1250 plus Ribociclib



D OP-1250 plus Alpelisib

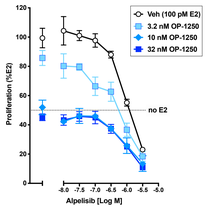


Figure 5. Cell proliferation of MCF-7 cells (A-C) and T47D cells (D) was measured after treatment with ligands after 6 days, as described in Figure 2.

OP-1250 shrinks tumors in the HCI-013 PDX model of mutant ERα that models endocrine resistant tumors

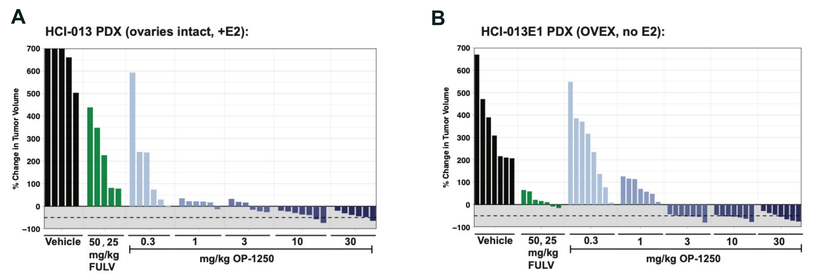


Figure 6. 28-day studies OP-1250 treatment in the HCI-013 PDX model, which contains $ESR1^{Y537S}$ mutation (A). Tumor growth was stimulated with E2 pellet and dosed with OP-1250 QD, while fulvestrant (Faslodex) was dosed QW (SC). Ovariectomized mice (B) were transplanted with a subline of the HCI-013 PDX line that grows in the absence of E2 supplementation.

OP-1250 shrinks tumors in multiple xenograft models at 3-10 mg/kg QD

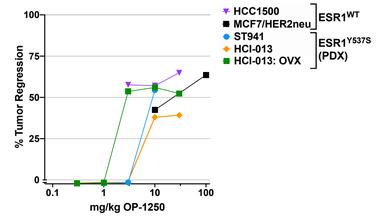


Figure 7. Comparison of administered dose of OP-1250 to observed tumor regression in multiple ERα wild type and mutant xenograft studies ranging from 24-49 days. Tumor regression = (1- mean (ending tumor volume – initial tumor volume) / initial tumor volume) *100.

10 mg/kg OP-1250 achieves high and stable levels in multiple species

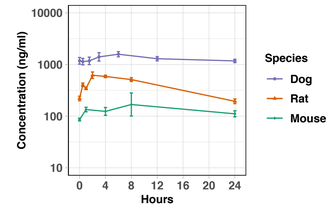


Figure 8. Serum concentrations of OP-1250 were measured after the final dose of 27-28 day multi-species studies with 10 mg/kg OP-1250, PO, QD.

Conclusions

- **OP-1250 is a complete ER-antagonist (CERAN) that blocks AF1 and AF2 of both wild type and mutant ERα.**
- **OP-1250 is orally bioavailable and achieves high and stable drug levels in multiple species.**
- **OP-1250 is a POTENT CERAN that shrinks tumors in both wild-type and mutant ESR1 xenograft models.**
- **OP-1250 is a promising new agent for the treatment of endocrine- resistant breast tumors.**

A phase 1 dose escalation and expansion study of OP-1250 alone, and in combination with a CDK4/6 inhibitor, and in combination with a PI3K alpha inhibitor in previously treated patients with ER+ metastatic breast cancer will be initiated in 2020.

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