OP-1250 is a Complete Estrogen Receptor Antagonist (CERAN) that Lacks Agonist Activity on Cell Signaling and Proliferation in Breast Cancer Cells

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The Estrogen Receptor (ER) is a tripartite protein with two distinct transcriptional activation functions (AF1 and AF2).

Partial antagonists (such as tamoxifen) have a short duration of response for treatment of breast cancer.

CERANs shut down both activation functions (AF1 and AF2) of the ER.

CERAN (a complete antagonist) in breast cancer and uterine cells AF1 is activated through signaling pathways. CERANs recruit N-CoR to inactivate AF1.

Myc, cyclinD1, BCL2, ...

DNA binding

AF1

mTOR PIk3 MAPK c-SRC EGFR FGFR IGFR

Estrogen (E2) turns on AF2. Myc, cyclinD1, BCL2, ...

AF1 on AF2

DNA binding

on

Signaling pathways turn on AF1. Both AF1 and AF2 mediate transcriptional activation functions (AF1 and AF2) of the ER.

Proliferation during Cancer Progression

mTOR PIk3 MAPK c-SRC EGFR FGFR IGFR

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References:

Partial agonists increase, or incompletely block, breast cancer cell proliferation

OP-1250 is a complete antagonist that turns off both AF1 and AF2 of the wild type and mutant ER

A

Alkaline phosphatase activity is dependent on AF1

B

Partial agonists, but not CERANs, activate AF1

CERANs like OP-1250 and Fulvestrant completely antagonize AF1 activity mediated by mutant ER

D

Conclusions and Clinical Significance of Complete ER Antagonism by OP-1250

- Recent experiments conducted by us and third parties in nonclinical models of breast cancer suggest that ER degradation, as achieved by many SERDs, on its own is not sufficient to effectively treat tumors and that the ability to completely inhibit ER function is best achieved through complete antagonism. Here we show in nonclinical studies that OP-1250 is a potent complete ER antagonism (CERAN) that completely inhibited breast cancer cell proliferation in multiple ER+ breast cancer cell lines.
- The expression of many genes that regulate proliferation, such as cyclin D1, are dependent on activation of AF1 of the ERs. Unlike partial agonists, OP-1250 completely turned off signaling through AF1 of ERs. Consequently, OP-1250 lacked agonist activity on the expression of genes involved in regulating a pro-potentiating and anti-apoptotic response.
- We previously reported that OP-1250 shrinks tumors in the HCl-013 PDX model of mutant ERs that models endocrine resistance.1 Here we show that OP-1250 was a complete antagonist of AF1 on Y337S and D538E mutants of ERs.
- OP-1250 is a potential new orally bioavailable agent for ER+ breast cancer. We have recently initiated a phase 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 endocrine therapy.