Complete Estrogen Receptor (ER) Antagonism As An Optimal Approach for ER-Positive Breast Cancer Drug Development

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Introduction

- Olema designed our lead compound (**OP-1250**) to be a complete estrogen receptor antagonist (CERAN) that blocks both transcriptional activation domains of the estrogen receptor (AF-1 and AF-2)

- OP-1250 consistently shrinks human estrogen receptor positive breast cancer xenografts whether implanted in the mammary fat pad or brain; an ability that traces to an excellent PK profile and its CERAN action

- Here we examined compounds that have been or are in clinical development for ER-positive breast cancer (whose structure has been disclosed), determined whether they are CERANs, and how CERANs versus non-CERANs compared in their ability to block breast cancer proliferation and degrade estrogen receptors

In the absence of estrogen, CERANs completely inactivate AF-1, while non-CERANs cannot

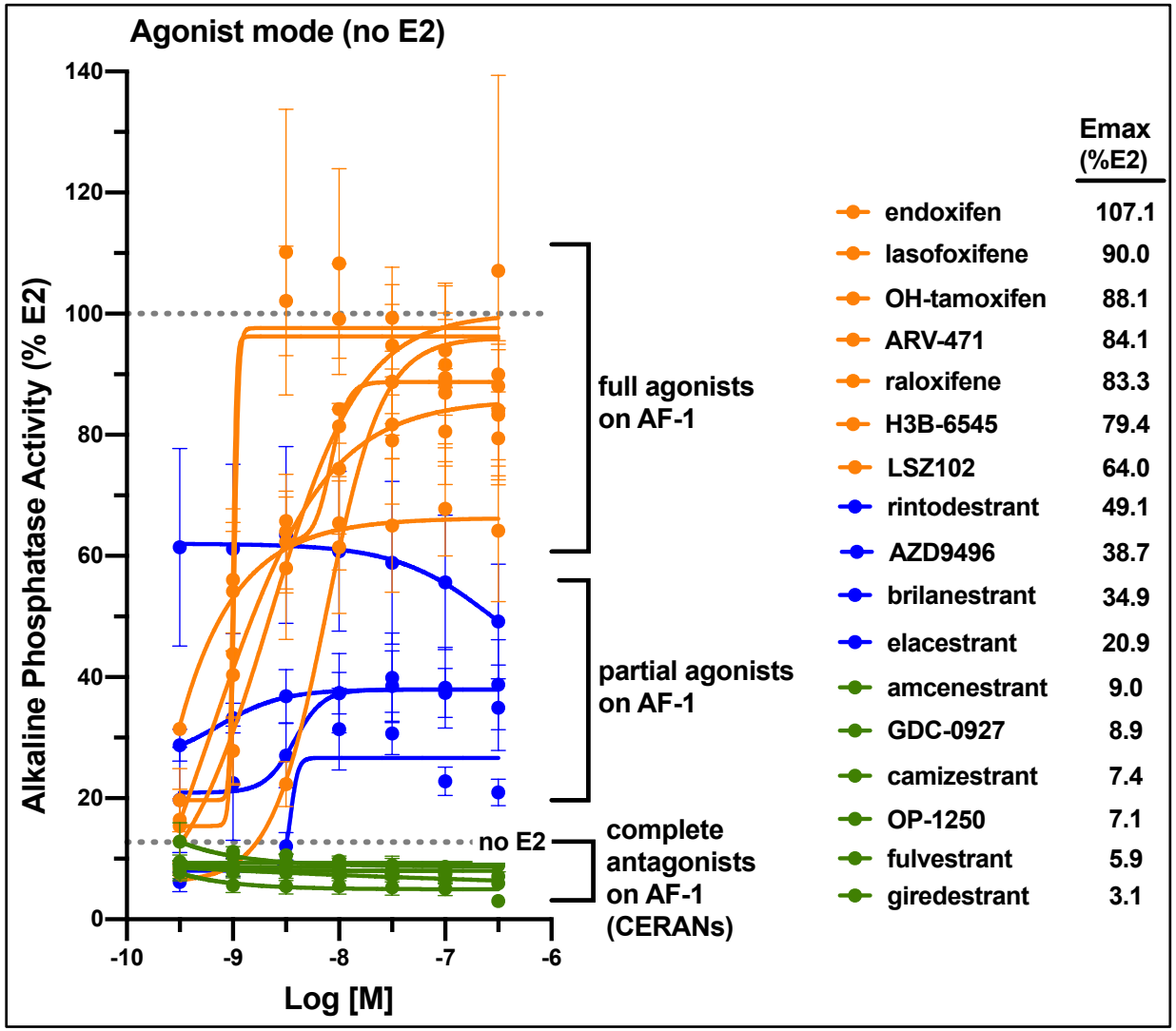


Figure 1. Endogenous activity of alkaline phosphatase stimulated by antiestrogens in the absence of estrogen. Shown are mean values normalized to E2 from 3 independent experiments.

- Alkaline phosphatase is an estrogen-responsive gene in ECC-1 cells driven by AF-1 action
- CERANs are defined by the Alkaline Phosphatase assay, a classic method of determining complete ER antagonism
- Unlike partial and full agonists, CERANs do not stimulate AF-1-dependent AP activity in the absence of estrogen
- CERANs completely inactivate AF-1

In the presence of estrogen, CERANs completely inactivate AF-1, while non-CERANs cannot

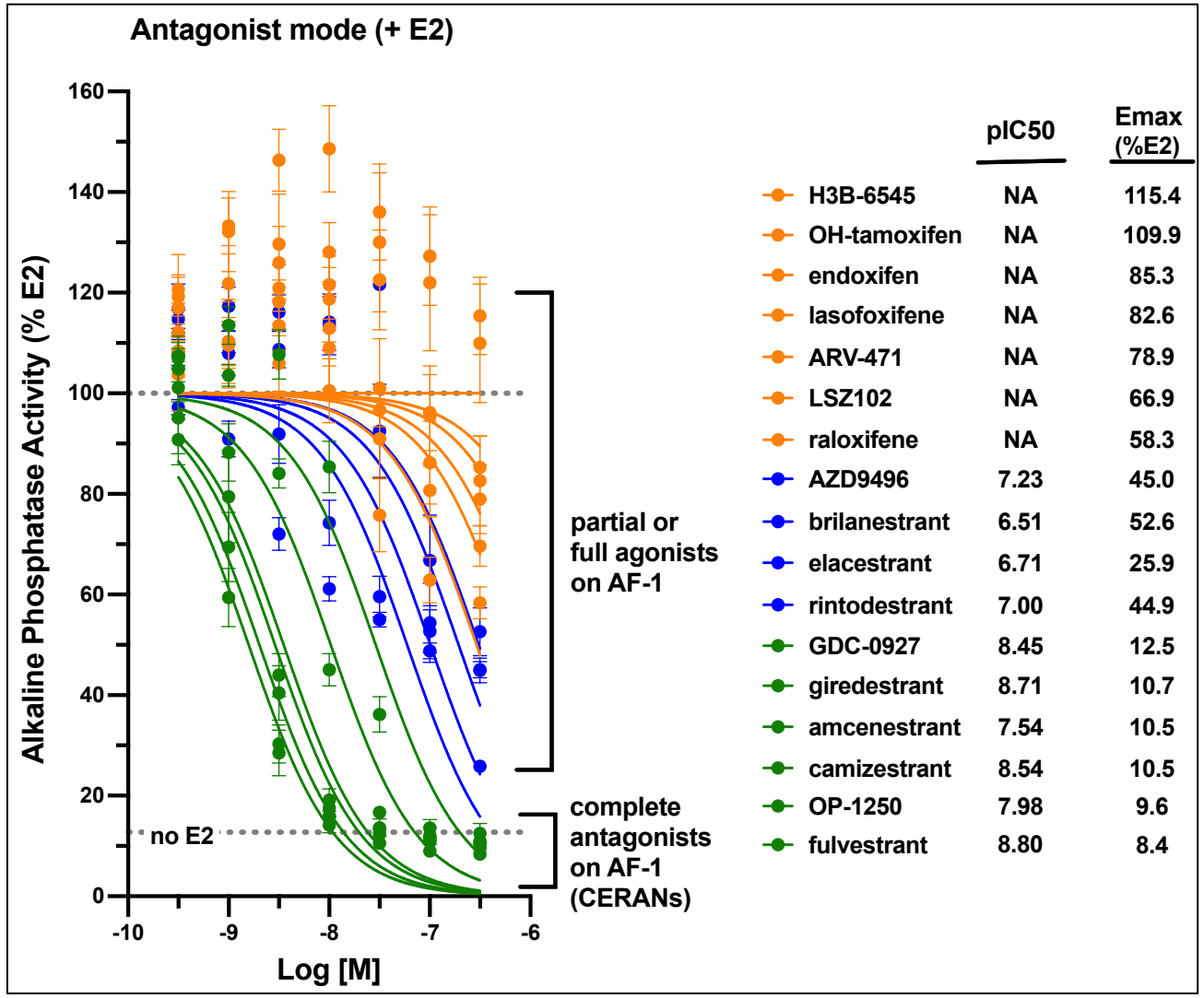
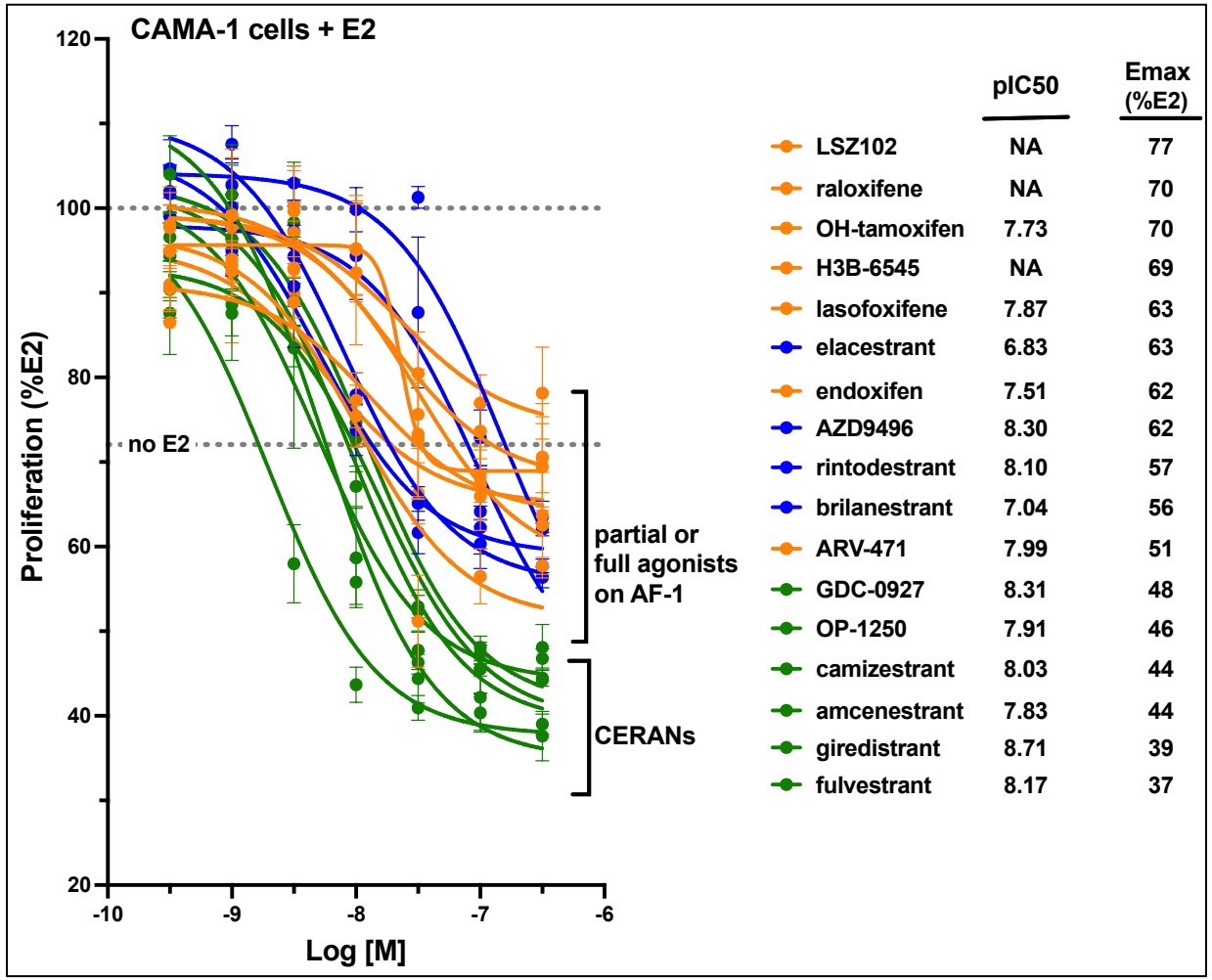


Figure 2. Endogenous activity of alkaline phosphatase stimulated by antiestrogens in the presence of 500 pM E2. Shown are mean values normalized to E2 from 3 independent experiments.

- The antagonist mode of the AP assay measures how these compounds block estrogen-stimulated AP activity

- CERANs completely antagonized AF-1 action in the presence of estrogen, while the non-CERANs cannot

CERANs more completely block estrogen-driven breast cancer proliferation than non-CERANs

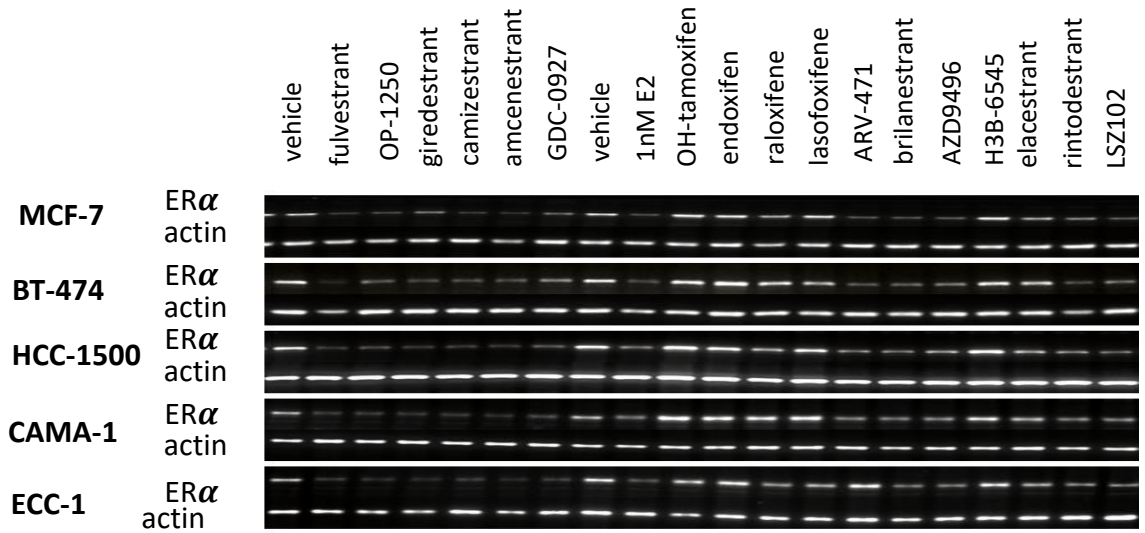


	pIC50	Emax (%E2)
LSZ102	NA	77
raloxifene	NA	70
OH-tamoxifen	7.73	70
H3B-6545	NA	69
lasofoxifene	7.87	63
elacestrant	6.83	63
endoxifen	7.51	62
AZD9496	8.30	62
rintodestrant	8.10	57
brilanestrant	7.04	56
ARV-471	7.99	51
GDC-0927	8.31	48
OP-1250	7.91	46
camizestrant	8.03	44
amcenestrant	7.83	44
giredistrant	8.71	39
fulvestrant	8.17	37

Figure 3. Proliferation of CAMA-1 breast cancer cells treated with antiestrogens for 6-8 days in the presence of 100pM E2 in E2-depleted media. Cell number was approximated using a DNA-binding dye. Shown are mean values normalized to E2 from 3 independent experiments.

- Inhibition of E2-driven proliferation in CAMA-1 cells distinguishes between CERANs and non-CERANs
- CERANs inhibited E2-driven proliferation to a greater degree than non-CERANs

CERANs reliably degrade ERα in multiple cell lines while non-CERANs have a variable degradation profile



- CERANs strongly degraded the ERα in all five ER+ cell lines tested
- Partial and full agonists variably and inconsistently degrade ERα
- Estradiol (E2), the prototypical agonist of ERα, degraded ERα in all five ER+ cell types tested

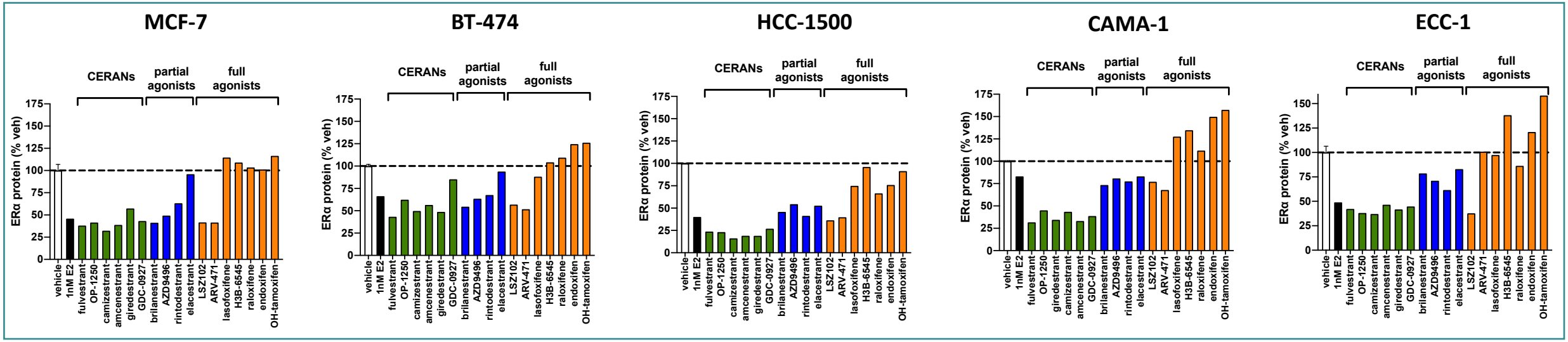


Figure 4. Immunoblot of ERα across multiple ER+ cell lines. Cells were incubated with 300nM compounds for 4h in estrogen-depleted media. Shown is the densitometry results of the immunoblot showing ERα protein levels relative to vehicle-treated cells after normalizing ERα to actin.

CERANs represent an optimal approach to antiestrogen drug development

- The antiestrogens investigated clustered into 3 distinct groups in an assay that detects ERα AF-1 action: complete ER antagonists (CERANs) and non-CERANs (full and partial agonists).
- CERANs more consistently degrade ERα across 5 different cell lines compared to partial or full agonists.
- CERANs more completely inhibit E2-driven proliferation of CAMA-1 breast cancer cells than non-CERANs. Because CERANs completely block ERα signaling we predict they will be more effective in treating and preventing breast cancer.

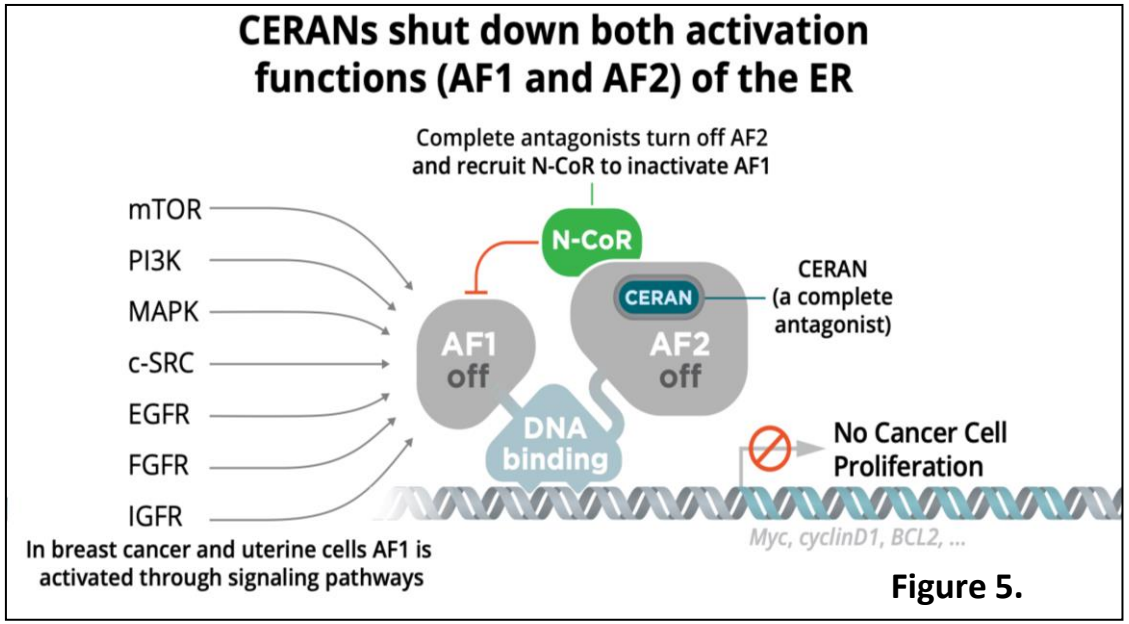


Figure 5.

Conclusion

OP-1250 is a promising new CERAN in the clinic for ER+ breast cancer that has numerous attractive drug features that distinguish it from other CERANs

- high bioavailability and favorable PK exposure, with steady-state plasma levels supporting once-daily oral dosing
- brain penetration
- accumulation in tumors
- preclinical safety profile that permits a starting human dose predicted to have efficacy

A phase I/II dose escalation and expansion trial of OP-1250 is in progress in patients with recurrent, locally advanced or metastatic ER+/HER2- breast cancer whose disease has progressed on prior endocrine therapy. Initial results expected Q4 2021.