Palazestrant Directly Recruits the Corepressor Protein NCoR1 in vitro Leading to Complete Antagonism of Estrogen Receptor Alpha

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Susanna A. Barratt, Guadalupe Peña, Chelsea Hope, Gopinath Palanisamy, Raymond A. Ng, David C. Myles

Olema Oncology, San Francisco, CA

Background

- Endocrine therapy (ET) remains the standard of care for estrogen receptor-positive (ER+) breast cancer, which accounts for ~80% of cases, yet limitations in the pharmacokinetics, efficacy, and tolerability of current agents highlight the need for improved options.[1,2]
- Palazestrant is a novel, orally bioavailable ET demonstrating favorable safety and efficacy and is currently being evaluated in two Phase III trials (OPERA-01, OPERA-02) for the treatment of ER+/human epidermal growth factor negative (HER2-) advanced breast cancer (NCT06016738, NCT07085767).[3,4]
- Palazestrant is a complete estrogen receptor antagonist (CERAN) and selective estrogen receptor degrader (SERD) that binds to the ER and suppresses estrogen-induced transcriptional activity (**Figure 1**).[5,6]

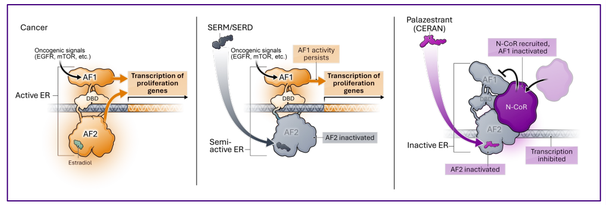
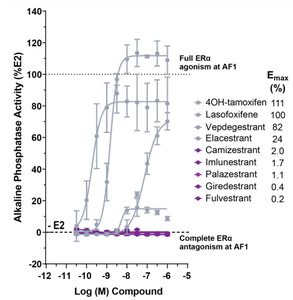


Figure 1: Differential effects of estradiol, selective estrogen receptor modulators (SERMs), and complete estrogen receptor antagonists (CERANs) on ERα-mediated gene transcription.

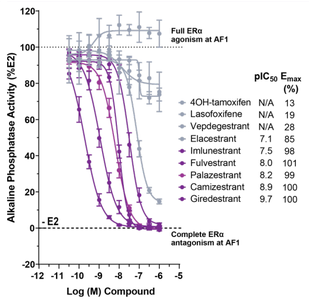
- Complete ER antagonists, including palazestrant, completely inactivate AF1 and AF2 activity of the estrogen receptor, while partial and strong agonists (SERMs) activate AF1 (**Figure 2**).

Activation of ER (AF1): Agonist Mode (- Estrogen)



	E_{max} (%)
4OH-tamoxifen	111
Lasofoxifene	100
Vepdegestrant	82
Elacestrant	24
Camizestrant	2.0
Imlunestrant	1.7
Palazestrant	1.1
Giredestrant	0.4
Fulvestrant	0.2

Inactivation of ER (AF1): Antagonist Mode (+ Estrogen)



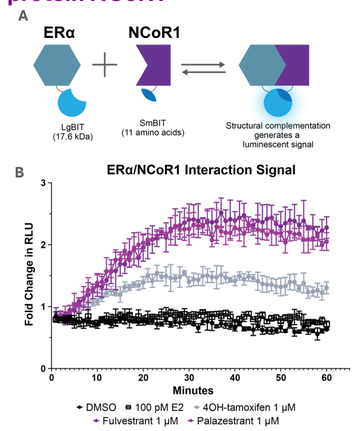
	pIC_{50}	E_{max} (%)
4OH-tamoxifen	N/A	13
Lasofoxifene	N/A	19
Vepdegestrant	N/A	28
Elacestrant	7.1	85
Imlunestrant	7.5	98
Fulvestrant	8.0	101
Palazestrant	8.2	99
Camizestrant	8.9	100
Giredestrant	9.7	100

Figure 2: Dose-response curves generated using an alkaline phosphatase induction assay in agonist mode (ligand only) and antagonist mode (ligand plus 500 mM E2).

Here, we report that palazestrant and other complete ER antagonists potently and completely recruit co-repressor protein NCoR1 to the ER as part of their mechanism of action.

Results

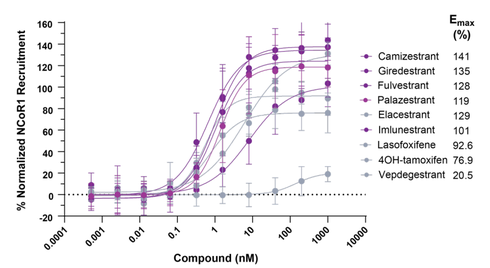
Palazestrant induces recruitment of co-repressor protein NCoR1



- A split-luciferase assay using full-length *ESR1*-LgBiT and full-length *NCoR1*-SmBiT fusion proteins was generated to enable dynamic monitoring of the NCoR1–ERα interaction (**Figure 3A**).
- Palazestrant and fulvestrant, complete ER antagonists, induced a strong increase in luminescence, indicating potent recruitment of NCoR1 to ERα (**Figure 3B**).
  - 4OH-tamoxifen treatment induced a limited increase in luminescence above vehicle or estradiol (E2) treatment that was much reduced in comparison.

Figure 3: Overview of the Promega NanoBiT® Protein-Protein Interaction Assay (**A**) and kinetic plot of fold-change in luminescence over time in HEK293 cells expressing *ESR1*-LgBiT and *NCoR1*-SmBiT treated with 1 µM of the indicated antiestrogens (**B**).

Palazestrant fully recruits NCoR1 to inactivate AF1, while SERMs demonstrate less potent or incomplete NCoR1 recruitment



	E_{max} (%)
Camizestrant	141
Giredestrant	135
Fulvestrant	128
Palazestrant	119
Elacestrant	129
Imlunestrant	101
Lasofoxifene	92.6
4OH-tamoxifen	76.9
Vepdegestrant	20.5

Figure 4: Dose-response curves of compound-induced NCoR1 recruitment to ERα in HEK293 cells expressing *ESR1*-LgBiT and *NCoR1*-SmBiT.

- Palazestrant and other antiestrogens that completely antagonize the ER (giredestrant, camizestrant, and fulvestrant) are the most potent and complete inducers of NCoR1 recruitment (**Figure 4**).
  - Palazestrant induces strong NCoR1–ERα recruitment at low concentrations (~1 nM).
  - 4OH-tamoxifen, lasofoxifene and vepdegestrant do not reach a maximum effect (E_{max}) of 100% indicating incomplete recruitment.
  - Elacestrant reaches E_{max} of 100% but at higher concentrations than palazestrant.

Palazestrant dose-dependently downregulates E2-driven expression of *PGR* and *GREB1*

- Palazestrant more potently suppresses key E2-target gene expression than 4OH-tamoxifen (at ≤1.6 nM) (**Figure 5A, B**).
  - *PGR* encodes the progesterone receptor, a nuclear hormone receptor with activity that can contributes to cell growth and metastasis.
  - *GREB1* encodes a coactivator of the ER and enhances its transcriptional activity.

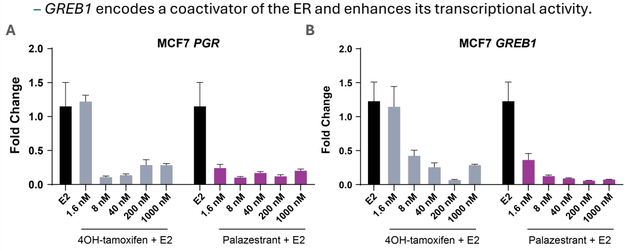


Figure 5: Dose-response fold-change expression of *PGR* (**A**) and *GREB1* (**B**) in MCF7 cells treated with 1.6, 8, 40, 200 or 1000 nM 4OH-tamoxifen or palazestrant plus 100 pM E2.

Palazestrant downregulates *PGR* and *GREB1* expression more robustly than SERMs in both *ESR1* wild-type and mutant ER+ breast cancer cells

- Palazestrant consistently downregulates *PGR* and *GREB1* expression in both *ESR1* wild-type (MCF7, CAMA-1) and mutant (ST941C) breast cancer models (**Figure 6A-F**).
- Antiestrogens that completely antagonize the ER downregulate *PGR* and *GREB1* expression more effectively than those with ER agonist activity (4OH-tamoxifen, elacestrant, lasofoxifene), and at low (nM) concentrations.

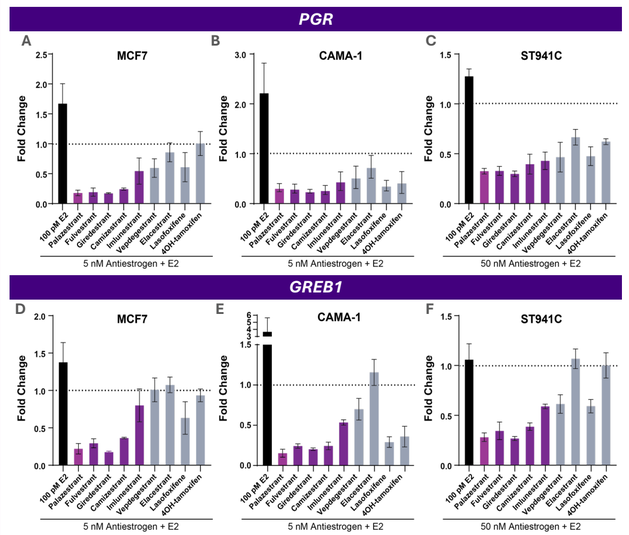


Figure 6: Fold-change expression of *GREB1* and *PGR* in MCF7 (**A**,**D**), CAMA-1 (**B**,**E**), and ST941C (**C**,**F**) cells treated with 5 or 50 nM antiestrogen plus 100 pM E2.

Complete antagonism of ERα results in a potent antiproliferation response

- Palazestrant and other complete ER antagonists do not cause proliferation of ER+ breast cancer models above vehicle under basal (no E2) conditions (**Figure 7**).
- 4OH-tamoxifen, lasofoxifene, and elacestrant (SERMs) increase proliferation of CAMA-1 and T47D cells above vehicle, indicating agonist-like activity.

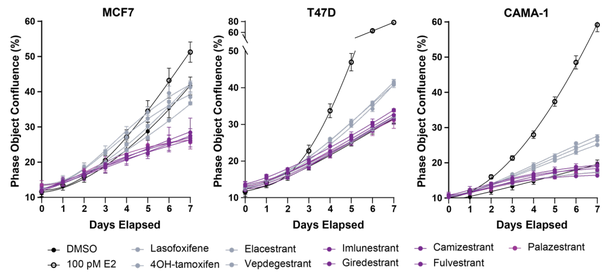
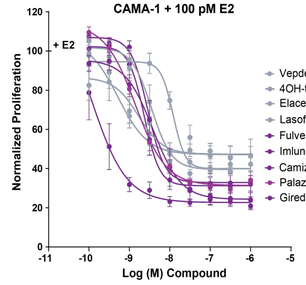


Figure 7: Growth curves for ER+ cell lines (MCF7, T47D, CAMA-1) treated with the indicated antiestrogen.



	IC_{50} (nM)	E_{max} (%)
Vepdegestrant	20	60
4OH-tamoxifen	11	53
Elacestrant	8.9	60
Lasofoxifene	6.6	53
Fulvestrant	6.1	76
Imlunestrant	5.1	67
Camizestrant	4.1	69
Palazestrant	3.6	69
Giredestrant	0.3	77

- Palazestrant and giredestrant demonstrate the most potent inhibition of proliferation in cells co-treated with E2 (**Figure 8**).
  - SERMs demonstrate reduced inhibition and potency.

Figure 8: Dose-response curve of cell proliferation following treatment with the indicated antiestrogen plus 100 pM E2.

Methods

ERα/NCoR1 NanoBiT®: HEK293 cells were transfected with *ESR1*-LgBiT and *NCoR1*-SmBiT in 3% charcoal-dextran–stripped serum (CDS). After 24 h, Nano-Glo® Live substrate was added and baseline luminescence recorded for 5 min. Compounds were then added and luminescence measured every minute for 60 min (kinetic) or at 2.5 h (dose-response). Data were normalized to untreated controls for fold-change and dose-response values normalized to 1 µM fulvestrant and vehicle controls.

qRT-PCR: MCF7, CAMA-1 and ST941C breast cancer cells ligand-treated for 24h in complete media, RNA isolated using QIAwave, and cDNA synthesized using the SuperScript™ IV First-Strand Synthesis System. Real time PCR was conducted using TaqMan probes and GAPDH as the internal control. Data represent mean +/- SD of experiments (n=3).

Cell Proliferation: MCF7, CAMA-1 and T47D breast cancer cells were ligand-treated for 7 days in media with 5% CDS. Cell number was assessed every 24 h by IncuCyte and at D0 and D7 by CyQUANT.

Conclusions

- **Palazestrant and other complete ER antagonists effectively recruit NCoR1 to ERα.**
  - **SERMs (4OH-tamoxifen, lasofoxifene) and the PROTAC vepdegestrant demonstrate incomplete NCoR1 recruitment.**
- **Palazestrant and other complete ER antagonists consistently demonstrate greater suppression of E2-driven *PGR* and *GREB1* expression compared to SERMs and PROTACs in both *ESR1* wild-type and mutant ER+ breast cancer models.**
- **Palazestrant and other complete ER antagonists fully inhibit cellular proliferation of ER+ breast cancer models, while SERMs (4OH-tamoxifen, lasofoxifene, and elacestrant) promote cellular growth in the absence of E2 through partial agonism of ERα.**
- **Palazestrant is a promising therapeutic strategy for treating ER+/HER2- breast cancer patients and is being evaluated clinically in two phase 3 trials, both as monotherapy and combination (NCT06016738, NCT07085767).**

References

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