A Phase I/II Open-label, First-in-Human, Multicenter, Dose Escalation and Dose Expansion Study of OP-1250 monotherapy in adult subjects with locally advanced, recurrent, and metastatic Hormone Receptor (HR)-positive, HER2-negative breast cancer (NCT04505826)

Erika Hamilton, M.D. (Sarah Cannon Research Institute/Tennessee Oncology) Carlos Alemany, M.D. (Advent Health Cancer Institute, Orlando FL) Nancy U Lin, M.D. (Department of Medical Oncology, Dana-Farber Cancer Institute, Boston MA) Trinh Le (Olema Oncology)
Peter Kushner, Ph.D. (Olema Oncology) Cyrus Harmon, Ph.D. (Olema Oncology) Pamela Klein, M.D. (Olema Oncology) Jo Anne Zujewski, M.D. (Olema Oncology) Manish Patel, M.D. (Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL)
Olema Oncology | 512 2nd Street | 4th Floor | San Francisco, CA 94107

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ABSTRACT #1167

Background

Endocrine therapy has been the primary treatment modality and the treatment of choice for HR+/HER2-metastatic breast cancer (MBC). Endocrine agents are administered sequentially, either in combination with targeted therapy or as monotherapy. The majority of patients with HR+/HER2- MBC will develop endocrine resistant disease. More effective and less toxic therapies are needed for the treatment of endocrine resistant disease.

OP-150 is a small molecule Complete Estrogen Receptor Antagonist (CERAN) that acts as a selective estrogen receptor degrader (SERD) and induces Estrogen Receptor (ER) degradation, completely inactivates the ER, blocks ER-driven transcriptional activity, and inhibits ER-driven breast cancer cell growth in non-clinical studies. OP-1250 demonstrates anti-cancer activity in vitro and in vivo, including activity against metastases in the brain and in tumors with activating mutations in *ESR1* in non-clinical studies. OP-1250 is orally bioavailable with a favorable pharmacokinetic profile supportive of once-daily dosing. OP-1250 is hypothesized to completely antagonize ER resulting in superior clinical outcomes compared to agents that only have partial antagonism of ER. Its favorable pharmacologic profile makes it an attractive agent for chronic use in patients with MBC.

OP-1250 is a Complete Estrogen Receptor Antagonist (CERAN)

Complete Antagonism of ER: Activity in both wild-type and mutant ESR1 models by turning-off both activating functional domains AF1 and AF2

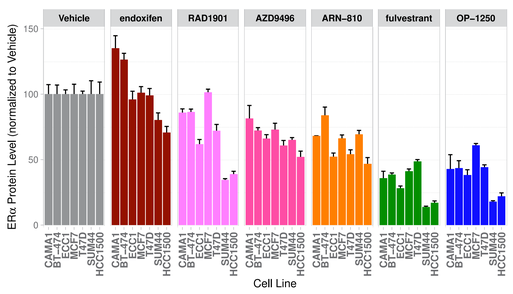
Strong Degradation of ER: Across all tested cell lines in a nonclinical analysis

Robust Tumor Shrinkage: Demonstrated in head-to-head nonclinical studies vs. fulvestrant, which only showed inhibition of tumor growth

CNS Penetration: Robust activity in nonclinical brain metastases studies

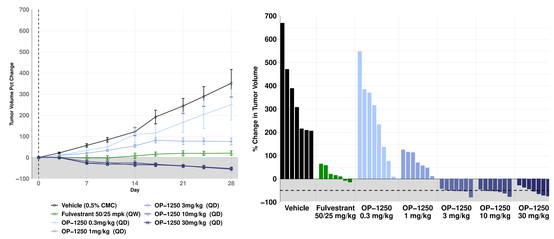
Favorable PK Profile: Daily oral dosing supported by PK modelling from nonclinical studies

OP-1250 robustly degrades ER in 7 tested cell lines



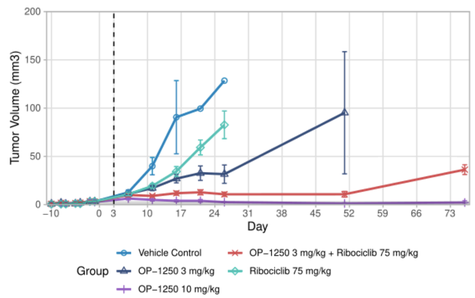
Hodges-Gallagher, L et al Development of OP-1250, an Oral Complete Estrogen Receptor Antagonist (CERAN) that shrinks ER-positive Breast Tumors in Xenograft models. SABCS PS-05-02 2019

OP-1250 shrinks HCI-013 (ESR1^{Y537S}) xenograft tumors at 3 mpk qd in ovariectomized mice (a model of postmenopausal women)



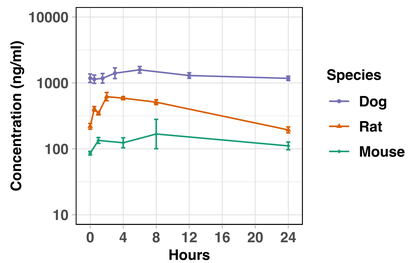
Hodges-Gallagher, L et al Development of OP-1250, an Oral Complete Estrogen Receptor Antagonist (CERAN) that shrinks ER-positive Breast Tumors in Xenograft models. SABCS PS-05-02 2019

OP-1250 shrinks mutant ESR1^{Y537S} brain tumors at 10 mg/kg



Hodges-Gallagher, L et al. OP-1250, an Oral Complete Estrogen Receptor Antagonist (CERAN) that penetrates the brain and prevents lethality from intracranial xenograft tumors expressing mutant ESR1, Abstract 4376, AACR 2020

Minimal peak-to-trough variation at steady state in 3 different species

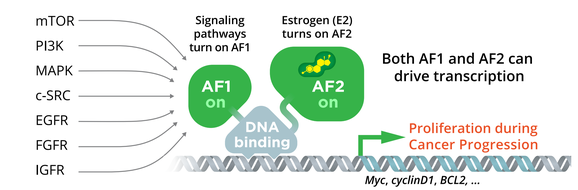


Hodges-Gallagher, L et al Development of OP-1250, an Oral Complete Estrogen Receptor Antagonist (CERAN) that shrinks ER-positive Breast Tumors in Xenograft models. SABCS PS-05-02 2019

Potent small molecule that both completely inactivates the estrogen receptor (ER) and strongly degrades ER *(based on nonclinical data)*

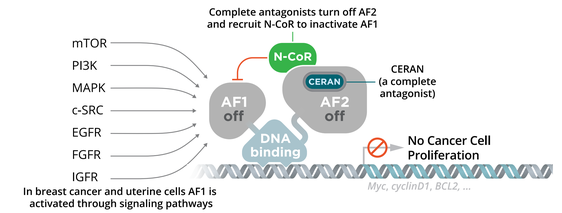
Mechanism of Action: Understanding the Estrogen Receptor (ER)

A Tripartite Protein with Two Distinct Transcriptional Activation Domains (AF1 and AF2)



Both AF1 and AF2 can drive transcription and cancer cell proliferation

CERANs Block AF1 and AF2 Activity Inhibiting Cell Proliferation



CERANs block AF1 activity, even in the presence of signaling, inhibiting cell proliferation

References:
Shang and Brown, Science, 29 Mar 2002: Vol. 295, Issue 5564, pp. 2465-2468
Webb, Nguyen, and Kushner, JBC, Vol. 278, 28 Feb 2003, pp. 6912–6920

Objectives

Part 1 (Dose Escalation)
- To identify the Dose Limiting Toxicity(s) (DLT), Maximum Tolerated Dose (MTD) and/or Recommended Phase II Dose (RP2D) of OP-1250
- To assess the safety and tolerability of OP-1250
- To assess the pharmacokinetics of OP-1250

Part 2 (Monotherapy Expansion)
2 expansion cohorts
- Measurable disease cohort
  - To estimate the clinical activity of OP-1250 in subjects with HR+/HER2- MBC who have no evidence of central nervous system (CNS) metastases.
- CNS Cohort
  - To estimate the clinical activity according to RECIST 1.1 and Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria

Eligibility: Selected Inclusion Criteria

- Males and females, age 18 or older, with ER+/HER2- recurrent, locally advanced or MBC who have had prior endocrine therapy
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- No oral endocrine therapy > 2 weeks prior to first dose
- Must not have received prior fulvestrant, chemotherapy, antibody therapy, or investigational therapy ≤ 4 weeks prior to the first dose
- Adequate hepatic function and renal function
- Normal coagulation panel
- Willingness to use effective contraception

Eligibility: Selected Exclusion Criteria

- Significant gastrointestinal, renal, cardiovascular, or any other co-morbidity that may interfere with participation in the trial
- Ongoing systemic bacterial, fungal, or viral infection (requiring antimicrobial therapy)
- Pregnancy or breastfeeding

OP-1250-001 Study Design

(ClinicalTrials.gov Identifier: NCT04505826)

Phase I/II open-label, 2-part, first-in-human study
- **Part 1:** Dose Escalation
  - Rolling 6 Design
- **Part 2:** Dose Expansion
  - 2 Expansion Cohorts
  - Recurrent, locally advanced or MBC patients with no evidence of central nervous system disease (CNS) metastasis
  - MBC with CNS metastasis

Treatment
- Oral, once a day dosing
- 28-day cycles

Correlative Science

- To determine biomarker expression, such as, ER, PR, Ki67 and others in the most recently obtained archival tumor tissue sample
- To evaluate whether ESR1 in circulating tumor DNA (ctDNA) can be correlated with response and/or activity of OP-1250
- To examine ctDNA pre- and post-therapy for mutESR1 and PIK3CA variants, and other relevant markers

Advent Health
Orlando, Florida,
United States, 32804
Contact: Ingrid Acker
407-303-2090
ingrid.acker@adventhealth.com

Florida Cancer Center
Sarasota, Florida,
United States, 34232
Contact: Heather Williams
941-377-9993
hmwilliams@flcancer.com

Sarah Cannon Research Institute
Nashville, Tennessee,
United States, 37203
Contact: Maddie Kolbe
615-524-4456
madison.kolbe@sarahcannon.com

For more information,
please contact
clinical@olemapharma.com

We thank all the patients and their families who have chosen to participate in this and other clinical trials.