AACR-NCI-EORTC Virtual International Conference on
MOLECULAR TARGETS AND CANCER THERAPEUTICS
October 7-10, 2021

A Phase 1/2 Dose Escalation and Expansion Study of OP-1250 in Adults with Advanced and/or Metastatic Hormone Receptor-positive (HR+), HER2-negative (HER2-) Breast Cancer (NCT04505826)

Carlos Alemany[1], Manish Patel[2], Zahi Mitri[3], Virginia Borges[4], Della Makower[5], Trinh Le[6], Pamela Klein[6], Julia Lawrence[6], Peter Kushner[6], Demiana Faltos[6], Cyrus Harmon[6], David Myles[6], JoAnne Zujewski[6], Erika Hamilton[7]

[1]AdventHealth Cancer Institute, Orlando, FL; [2]Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL; [3]Knight Cancer Institute OHSU, Portland, OR; [4]University of Colorado, Denver, CO; [5]Montefiore Medical Center, New York, NY; [6]Olema Oncology, San Francisco, CA; [7]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN

Carlos Alemany, MD

Director of Clinical Research

AdventHealth Cancer Institute

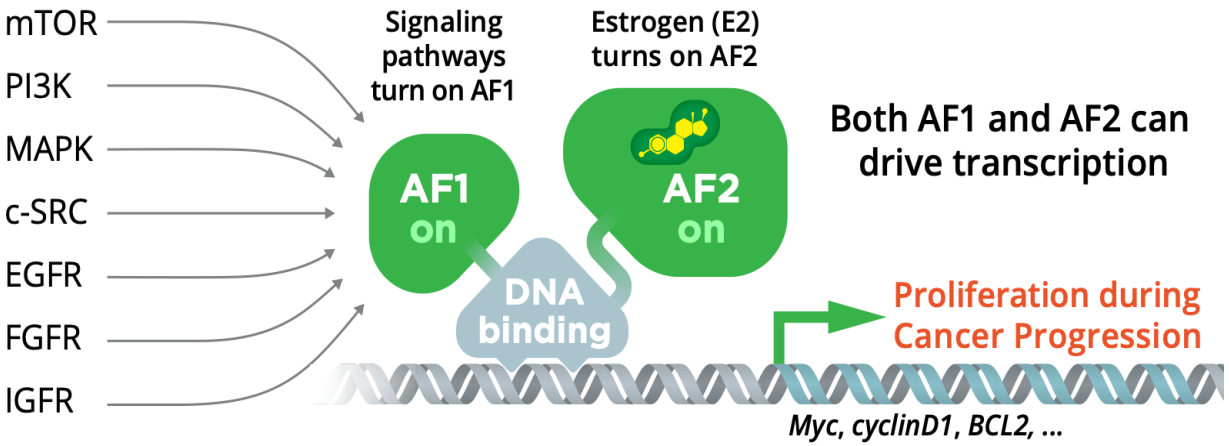
I have the following financial relationships to disclose:

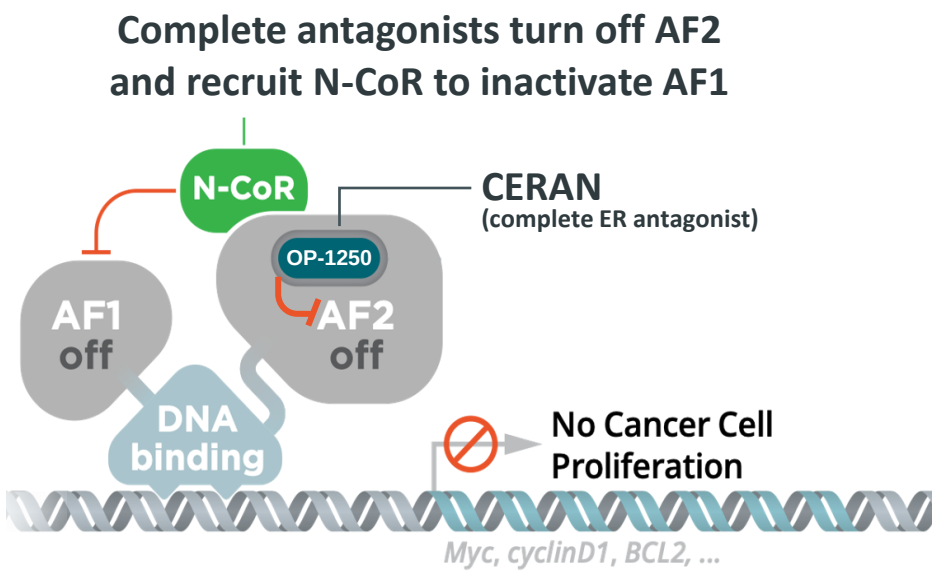
- **Consultant for:** none
- **Speaker's Bureau for:** Alexion, BMS
- **Grant/Research support from:** Genentech, BMS, Astra Zeneca, Sanofi, Seagen, Merck, Janzen, Amgen, Celgene, Olema
- **Stockholder in:** none
- **Employee of:** none

I will discuss the following investigational product in my presentation: OP-1250

OP-1250, a Complete Estrogen Receptor ANtagonist (CERAN)

OP-1250 potently and completely inactivates the Estrogen Receptor (ER), blocks ER-driven transcriptional activity, inhibits ER-driven breast cancer cell growth, and strongly induces degradation of ER





AF1: activation factor 1
AF2: activation factor 2

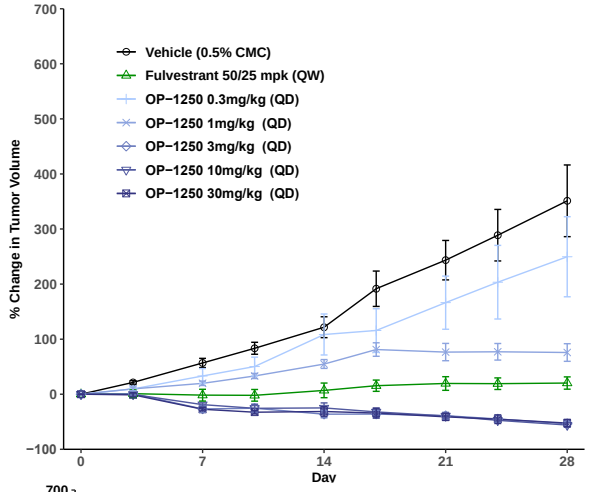
References: Shang and Brown, Science, 29 Mar 2002: Vol. 295, Issue 5564, pp. 2465-2468 ; Webb, Nguyen, and Kushner, JBC, Vol. 278, 28 Feb 2003, pp. 6912–6920

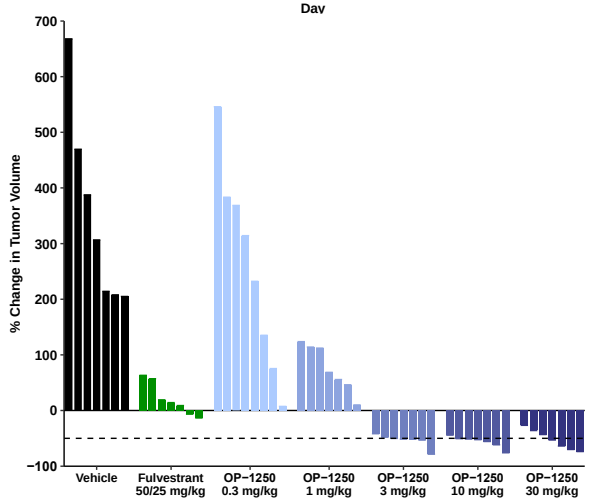
Background and Rationale

- Estrogen receptor (ER) is a key therapeutic target for ER+/HER2-metastatic breast cancer (MBC)
- Despite the effectiveness of available endocrine therapies, most patients will ultimately develop endocrine-resistant disease. More effective and less toxic therapies are needed
- OP-1250, a CERAN (Complete Estrogen Antagonist) has demonstrated preclinically:
  - Complete ER antagonism with blockade of AF1 and AF2 transcriptional activation domains
  - Robust anti-tumor efficacy in multiple preclinical models, including in wildtype, ESR1 and PI3KA mutations
    - In nonclinical studies, OP-1250 reduced tumor size while fulvestrant only slowed tumor growth
  - Strong degradation of ERα across all tested cell lines
  - High oral bioavailability and favorable pharmacokinetic (PK) exposure, with steady-state plasma levels supporting convenient, once-daily oral dosing
  - CNS penetration, with promising nonclinical data in treating brain metastases

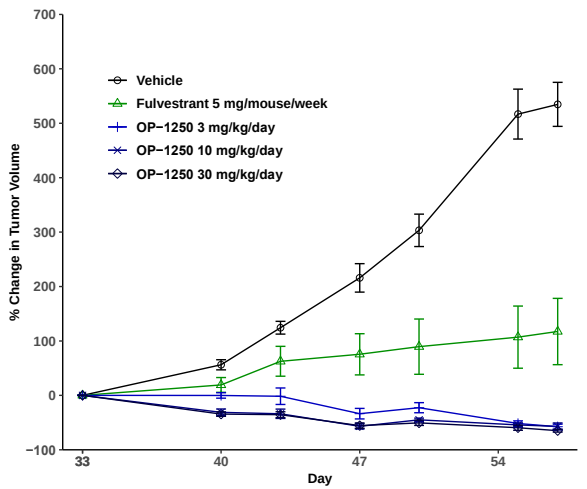
OP-1250 Demonstrated Robust Tumor Shrinkage Across Multiple Xenograft Models

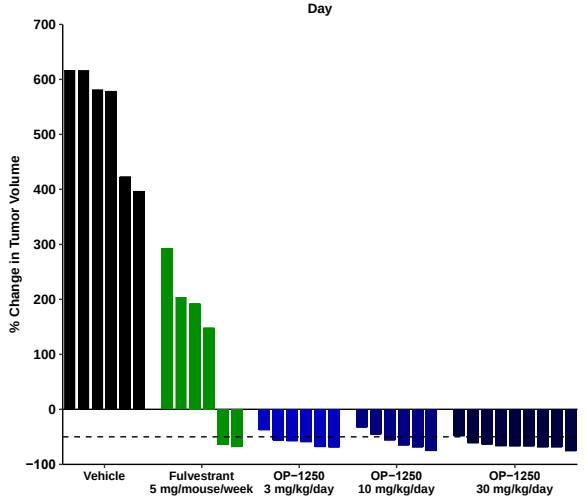
HCI-013EI (ESR1^{Y537S})



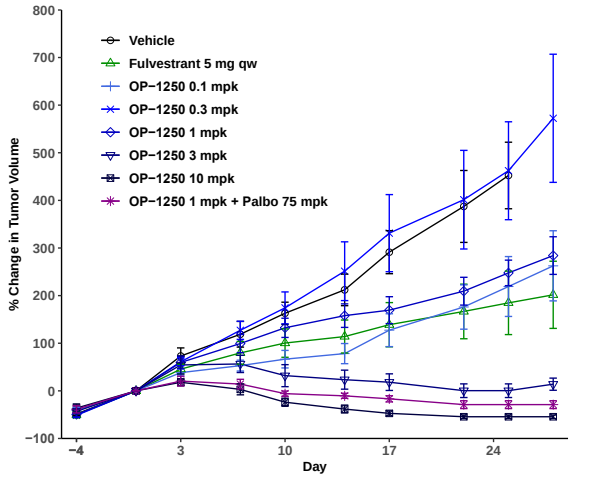


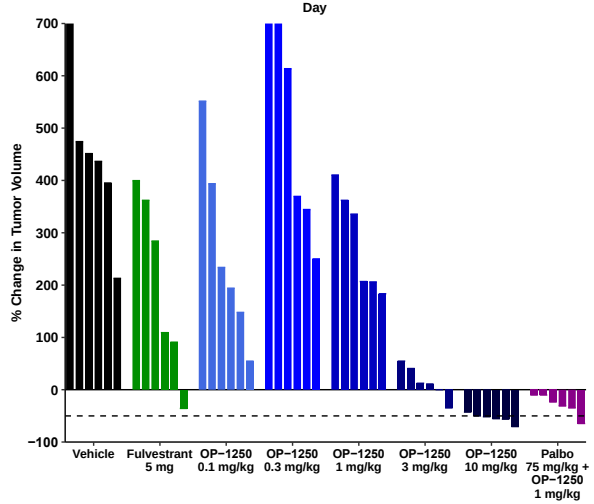
HCC1500 (ESR1 wild-type)





ST941 (ESR1^{Y537S})

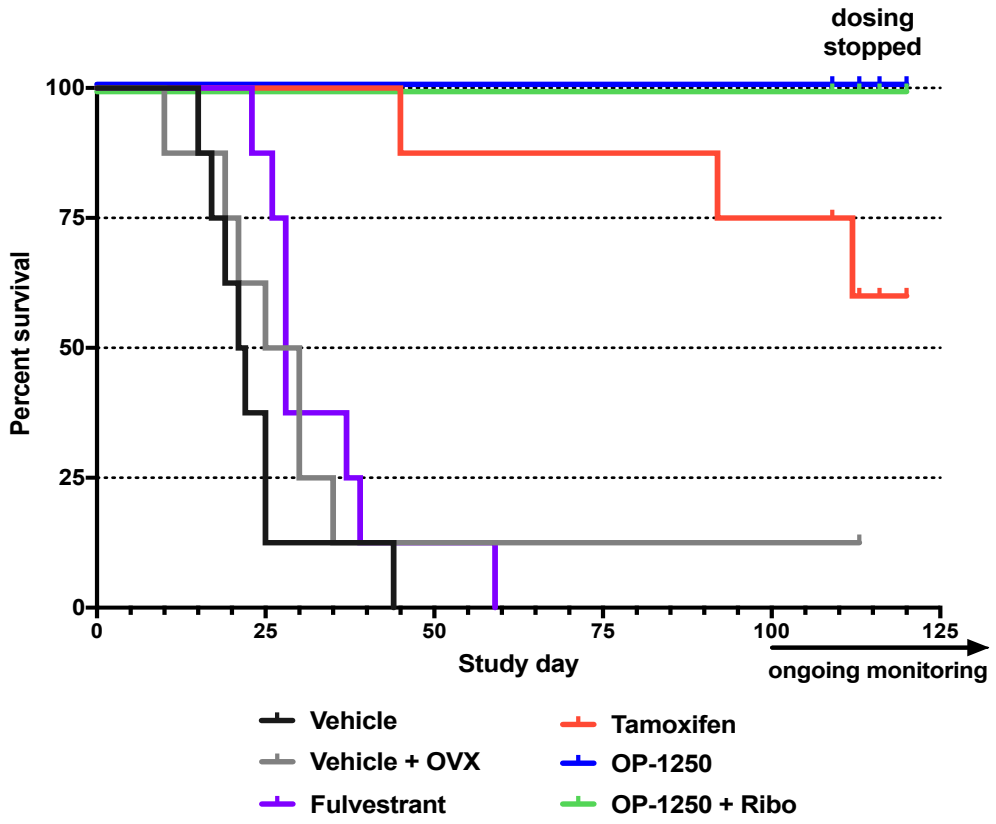




References: Hodges-Gallagher et al., Abstract P5-05-02, Abstracts: 2019 San Antonio Breast Cancer Symposium; December 10-14, 2019; San Antonio, Texas ; Hodges-Gallagher et al., Abstract 4376, Proceedings: AACR Annual Meeting 2020; April 27-28, 2020 and June 22-24, 2020; Philadelphia, PA

OP-1250 Prolonged Survival Impact in ER+ MBC Brain Metastases Model

OP-1250 vs. Fulvestrant and Tamoxifen: Prolonged Survival Impact

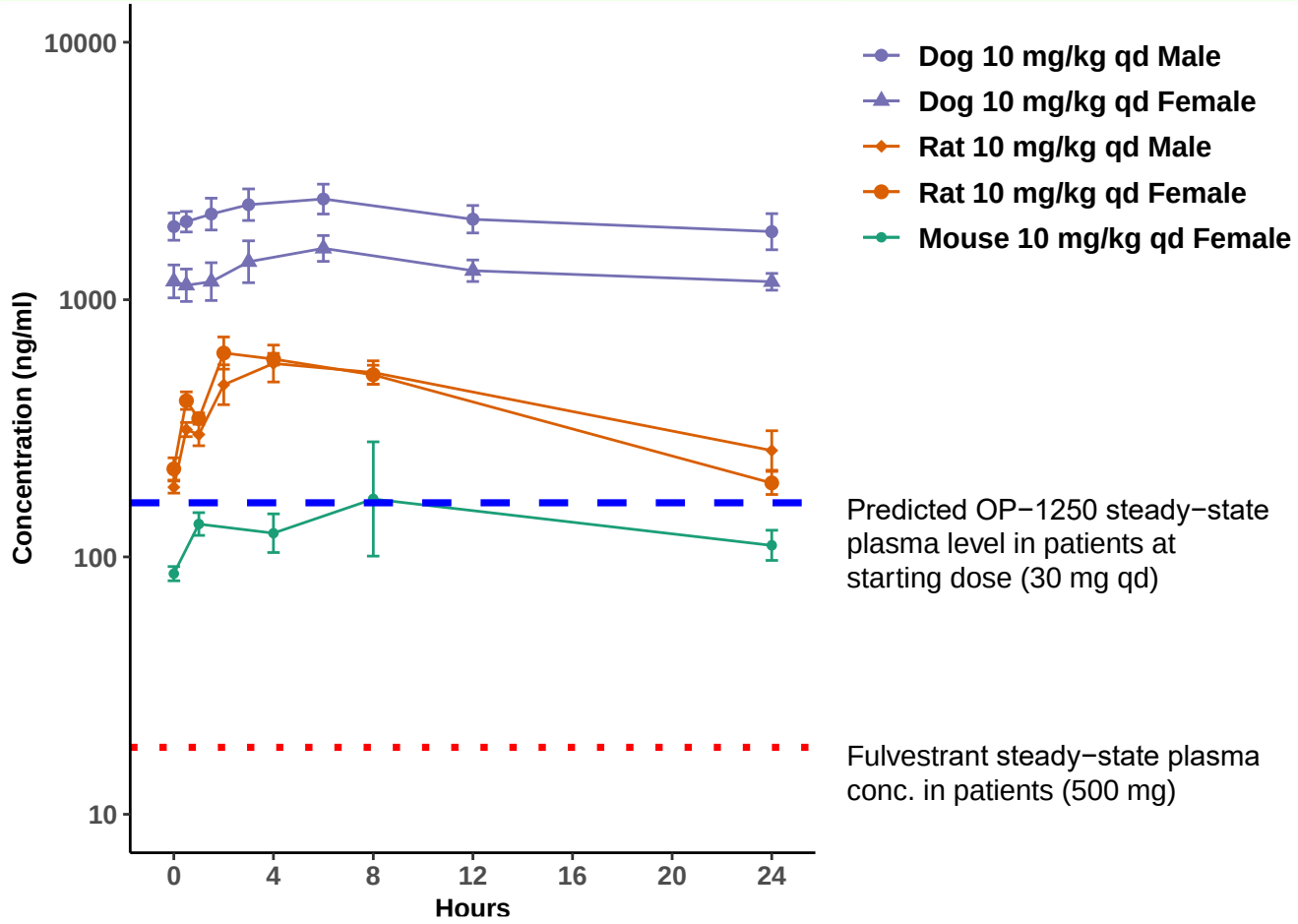


- Dosing stopped in OP-1250 10 mg/kg group at 100 days
- OP-1250 prevented death in all animals at day 120. Data suggest that OP-1250 may be an active treatment for patients with brain metastasis from ER+ breast cancer.

OP-1250 was superior in shrinking ER+ tumors compared to other endocrine therapies tested, including fulvestrant and tamoxifen

Reference: Hodges-Gallagher et al., Abstract 4376, Proceedings: AACR Annual Meeting 2020; April 27-28, 2020 and June 22-24, 2020; Philadelphia, PA

OP-1250 is Orally Bioavailable with Attractive Steady-State Plasma Levels



- Steady-state plasma levels relatively constant through 24-hour period
- Profile consistent with daily oral dosing in humans

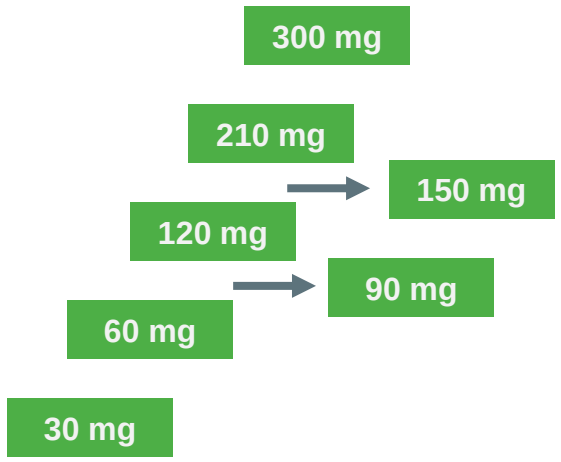
Minimal peak-to-trough variation at steady state in 3 different species

Reference: Hodges-Gallagher et al., Abstract P5-05-02, Abstracts: 2019 San Antonio Breast Cancer Symposium; December 10-14, 2019; San Antonio, Texas

OP-1250-001: First in Human Phase I/II Clinical Study

OP-1250 oral, once-daily dosing

Phase Ia Dose Escalation



- Rolling 6 design
- Intermediate dosing to evaluate smaller step-ups in targeted dose range

Phase Ib Dose Expansion

Dose 1

Dose 2

→ RP2D

- 1 or 2 dose cohorts, each N=15
- Patients with measurable disease
- Allows for further evaluation of 2 potential candidate Recommended Phase II Dose (RP2D)
- Findings will inform selection of RP2D

Phase II Cohorts

- Cohort A
- Cohort B
- Cohort C

Cohort A, B, and C

- Patients with measurable disease (N=50)
- Patients with non-measurable disease (N=15)
- Patients with CNS metastasis (N=15)

OP-1250-001: Objectives

- Open-label, Phase I/II clinical trial designed to evaluate OP-1250, administered orally once-daily in patients with ER+/HER2- recurrent, locally advanced or MBC who have had prior endocrine therapy

Study Objectives

Phase	Primary Objectives	Secondary and Exploratory Objectives
Phase Ia, **Dose Escalation** Phase Ib, **Dose Expansion**	▪ Pharmacokinetics ▪ Safety and tolerability ▪ Identify RP2D	▪ Anti-tumor efficacy ▪ Biomarker expression ▪ ESR1 in circulating tumor DNA (ctDNA)
Phase II **Expansion**	▪ Anti-tumor activity in measurable disease cohort ▪ Safety and tolerability at RP2D	▪ Clinical benefit in non-measurable disease and CNS metastasis ▪ ctDNA for *mut*ESR1 ▪ ER, PR and Ki67 in archival and serial biopsies

Key Inclusion Criteria

- Adults with ER+/HER2- recurrent, locally advanced or MBC
- At least 1 prior hormonal regimen for locally advanced or metastatic disease

Additional Criteria by Phase			
• Phase Ia, **Dose Escalation**	▪ ≤ 2 prior chemotherapy regimens for locally advanced or metastatic disease ▪ Evaluable disease (measurable and non-measurable disease are eligible)		
• Phase Ib, **Dose Expansion** • Phase II, **Expansion**	▪ Measurable disease by RECIST 1.1 criteria ▪ ≤ 1 prior chemotherapy regimen for locally advanced or metastatic disease ▪ ≤ 4 prior endocrine-based therapies for locally advanced or metastatic disease		
• Phase II, Dose Expansion • Cohort-based criteria	Cohort A: ▪ Measurable disease	Cohort B: ▪ Non-measurable	Cohort C: ▪ CNS disease ▪ ≤ 3 prior chemotherapy regimens for locally advanced or metastatic disease ▪ Evaluable disease

Summary

- OP-1250, a novel CERAN (Complete Estrogen Receptor Antagonist), has the potential to be a best-in-class endocrine therapy
- OP-1250 is currently in being studied in a Phase I/II First-in-Human Clinical Trial in patients with ER+/HER2- metastatic breast cancer
- The key objectives of the study are to assess:
  - Safety, pharmacokinetics and identification of a RP2D
  - Preliminary efficacy
  - Serial evaluation of ESR1 and other relevant genetic mutations in ctDNA
- The Phase Ia OP-1250-001 dose escalation, utilizing a rolling 6 design and allowing for intermediate dose levels, will be highly informative across multiple dose levels within the predicted targeted range for a RP2D
- Preliminary efficacy will be obtained across 3 Phase II patient cohorts (patients with measurable disease, patients with non-measurable disease, and patients with CNS metastasis), reflective of an ER+/HER2-metastatic breast cancer population
- Initial data from the Phase Ia dose-escalation stage anticipated in Q4 2021
- Contact: clinical@olema.com (NCT04505826)