Background
Endocrine therapy has been the primary treatment modality and the treatment of choice for HR+ HER2- metastatic breast cancer (MBC). Estrogens act as a selective estrogen receptor degrader (SERD) and induces Estrogen Receptor (ER) degradation, completely inactivates the ER, blocks receptor transcriptional activity, and inhibits ER-driven breast cancer cell growth. In clinical studies, OP-1250 demonstrates anti-cancer activity in vitro and in vivo, including activity against ERα-mutant tumors in the presence of PI3K inhibition, which has been observed in patients with HR+/HER2- mASTS.

OP-1250 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 receptor transcriptional activity, and inhibits ER-driven breast cancer cell growth in in vitro and in vivo. OP-1250 is highly selective for the ER, which is the target of interest, and shows no activity against other estrogen receptors.

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

OP-1250 shrinks mutant ESR1-Y537S xenograft tumors at 3 mpq in ovariectomized mice (a model of postmenopausal women)

Mechanism of Action: Understanding the Estrogen Receptor (ER)

CERANs shut down both activation functions (AF1 and AF2) of the ER and recruit N-CoR to inactivate AF1 resulting in superior clinical outcomes compared to agents that have only partial antagonism of ER. This 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 functional domains AF1 and AF2.

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

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

CNS Penetration: Robust activity in nonclinical breast metastases studies.

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

OP-1250 robustly degrades ER in 7 tested cell lines

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

Objectives

Part 1 (Dose Escalation)
- To identify the Dose Limiting Toxicity (DLT), Maximum Tolerated Dose (MTD) and/or Recommended Phase 2 Dose (RP2D) of OP-1250
- To assess the safety and tolerability of OP-1250
- To assess the pharmacokinetics of OP-1250

Part 2 (Dose Expansion)
2 expansion cohorts
- Measurable disease cohort
  - To estimate the clinical activity of OP-1250 in subjects with HR+/HER2- MBC who have evidence of central nervous system (CNS) metastases
  - OCB Cohort
  - To estimate the clinical activity according to RECIST 1.1 and Response Assessment in Neuro-Oncology Brain Metastases (RAIN-OBM) 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 more than two prior lines of therapy and no prior progression on the most recent prior therapy
- Must have received prior endocrine therapy on the prior therapy
- Adequate hematologic and renal function
- Normal coagulation panel
- Willingness to use contraception

Eligibility: Selected Exclusion Criteria

- Pregnancy or breastfeeding
- Normal coagulation panel
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- No more than two prior lines of therapy and no prior progression on the most recent prior therapy
- Must have received prior endocrine therapy on the prior therapy
- Adequate hematologic and renal function
- Normal coagulation panel
- Willingness to use contraception

Correlative Science

- To determine biomarker expression, such as ER, HER2, and others in the most recently obtained archival tumor tissue sample
- To evaluate whether ER 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

OP-1250-001 Study Design

ClinicalTrials.gov identifier: NCT04450301

Phase II open-label, 2-part, first-in-human study
- Part 1: Dose Escalation - Building Dose
- Part 2: Dose Expansion - 2 Expansion Cohorts

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