

OPERA-01: A randomized, open-label, phase 3 study of palazestrant (OP-1250) monotherapy vs standard-of-care endocrine therapy for patients with ER+, HER2- advanced breast cancer after endocrine and CDK4/6 inhibitor therapy



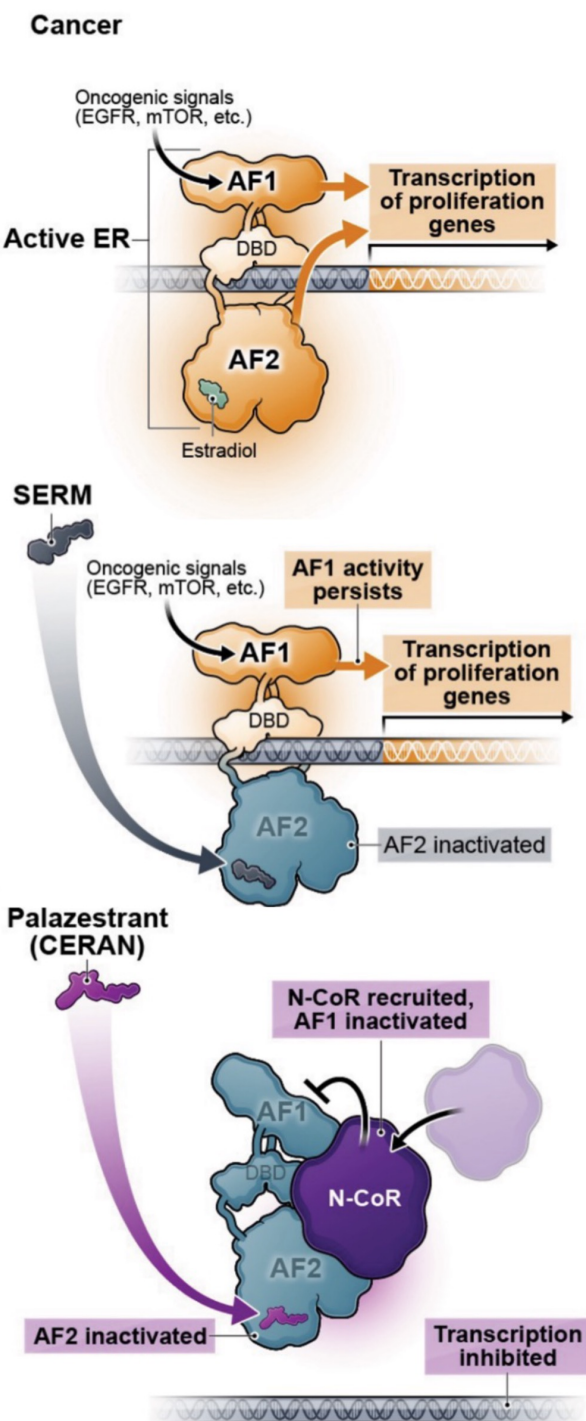
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BACKGROUND

- Endocrine therapy (ET) resistance is a major challenge when treating estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer; estrogen receptor (*ESR1*) mutations are an important mechanism of resistance.¹
- The standard-of-care (SOC) first-line treatment for ER+, HER2- metastatic breast cancer (MBC) is ET plus a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i).² Despite the benefit of ET and CDK4/6i, disease progression and acquired resistance to the combination occurs in most patients with ER+, HER2- MBC. Novel and more effective ETs that can overcome resistance are needed to improve outcomes and delay time to chemotherapy.
- Palazestrant is a novel oral complete estrogen receptor antagonist (CERAN) and selective estrogen receptor degrader (SERD), that blocks both transcriptional activation function domains, AF1 and AF2, resulting in complete inhibition of ER-driven transcription regardless of *ESR1* mutation status.

Figure 1: Mechanism of Action of Palazestrant (OP-1250)³



AF, activation function; CERAN, complete estrogen receptor antagonist; DBD, DNA binding domain; EGFR, epidermal growth factor receptor; ER, estrogen receptor; mTOR, mammalian target of rapamycin; N-CoR, nuclear receptor corepressor; SERM, selective estrogen receptor modulator.

- In early-phase trials, palazestrant was well tolerated, with favorable pharmacokinetics supporting once-daily dosing; it also showed antitumor activity and combinability with palbociclib⁴ and ribociclib.⁵
- As monotherapy, palazestrant showed a tolerable safety profile, favorable pharmacokinetics and encouraging antitumor efficacy in heavily pretreated patients during phase 1/2 studies, regardless of *ESR1* mutation status (NCT04505826).⁶

OPERA-01: STUDY DESIGN & ELIGIBILITY

OPERA-01 is an international, multicenter, randomized, open-label, active-controlled, phase 3 study (NCT06016738)

- The study will compare the safety and efficacy of palazestrant to the SOC options of fulvestrant or an aromatase inhibitor (letrozole, anastrozole, or exemestane) in women and men with advanced breast cancer (ABC) whose disease has advanced on ET in combination with a CDK4/6i.

Key eligibility criteria:

- ER+, HER2- advanced breast cancer
- Evaluable disease (measurable or evaluable bone disease)
- 1-2 prior lines of endocrine therapy for ABC
- Prior treatment with a CDK4/6 inhibitor

N = 470

Palazestrant 90 mg

SOC ET[†]

Treatment until disease progression or intolerable toxicity

Dosing schedule: 28-day cycle; palazestrant (oral once daily)

Stratification factors:

- ESR1*-mut or *ESR1*-mut-nd, assessed centrally on ctDNA collected during screening period
- Prior lines of ET for advanced disease (1 vs 2)
- Presence of visceral disease (yes vs no)

The study included the dose selection part where approximately 120 patients were randomized between 90 mg QD palazestrant, 120 mg QD palazestrant, or SOC ET. The dose of palazestrant 90 mg was selected based on safety, efficacy, pharmacokinetics, and patient-reported outcomes. Out of 510 patients to be enrolled in total, 470 patients will be randomized between 90 mg QD palazestrant or SOC ET.

[†]Fulvestrant 500 mg IM on day 1 of each 28-day cycle, with an additional dose on day 15 of cycle 1 (recommended for patients who had not previously received fulvestrant), anastrozole 1 mg (oral once daily), letrozole 2.5 mg (oral once daily), and exemestane 25 mg (oral once daily). GnRH agonist requested for premenopausal women and for men.

ABC, advanced breast cancer; CDK4/6, cyclin-dependent kinase 4/6; ctDNA, circulating tumor DNA; ER+, estrogen receptor-positive; *ESR1*-mut, estrogen receptor 1 mutation; *ESR1*-mut-nd, estrogen receptor 1 mutation not detected; ET, endocrine therapy; GnRH, gonadotropin-releasing hormone; HER2-, human epidermal growth factor receptor 2-negative; IM, intramuscular; MBC, metastatic breast cancer; pt, patient; QD, once a day; SOC, standard-of-care.

Key Inclusion Criteria:

- Adult female or male patients
- ER+, HER2- locally advanced or metastatic breast cancer that is not amenable to curative therapy
- Evaluable disease (measurable per RECIST v1.1 or evaluable bone disease)
- Previously received and progressed on 1 or 2 ET lines in the advanced setting:
 - One ET line must be in combination with a CDK4/6i
 - Duration of the most recent ET line must be ≥6 months
- ECOG Performance Status of 0 or 1
- Adequate hematologic, hepatic, and renal functions
- Female patients can be pre-, peri-, or postmenopausal
- Male and pre- or perimenopausal female patients must be willing to take a gonadotropin-releasing hormone (GnRH) agonist during treatment

Key Exclusion Criteria:

- Symptomatic visceral disease, imminent organ failure, or any disease burden that makes the patient ineligible for endocrine monotherapy
- Received prior chemotherapy in the advanced/metastatic setting
- Any contraindications to the selected SOC ET in the local prescribing information
- Symptomatic central nervous system (CNS) metastases, carcinomatous meningitis, leptomeningeal disease, or a spinal cord compression that requires immediate CNS-directed treatment
- Clinically significant comorbidities, such as significant cardiac or cerebrovascular disease, or gastrointestinal disorders that could affect absorption of study treatment
- Active infection or at a high risk of developing serious infection during study treatment
- Have received a prior elacestrant or experimental SERD

ENDPOINTS

Primary endpoints

- PFS, as assessed by BIRC, in the *ESR1*-mut population
- PFS, as assessed by BIRC, in the *ESR1*-mut-nd population

Key secondary endpoints

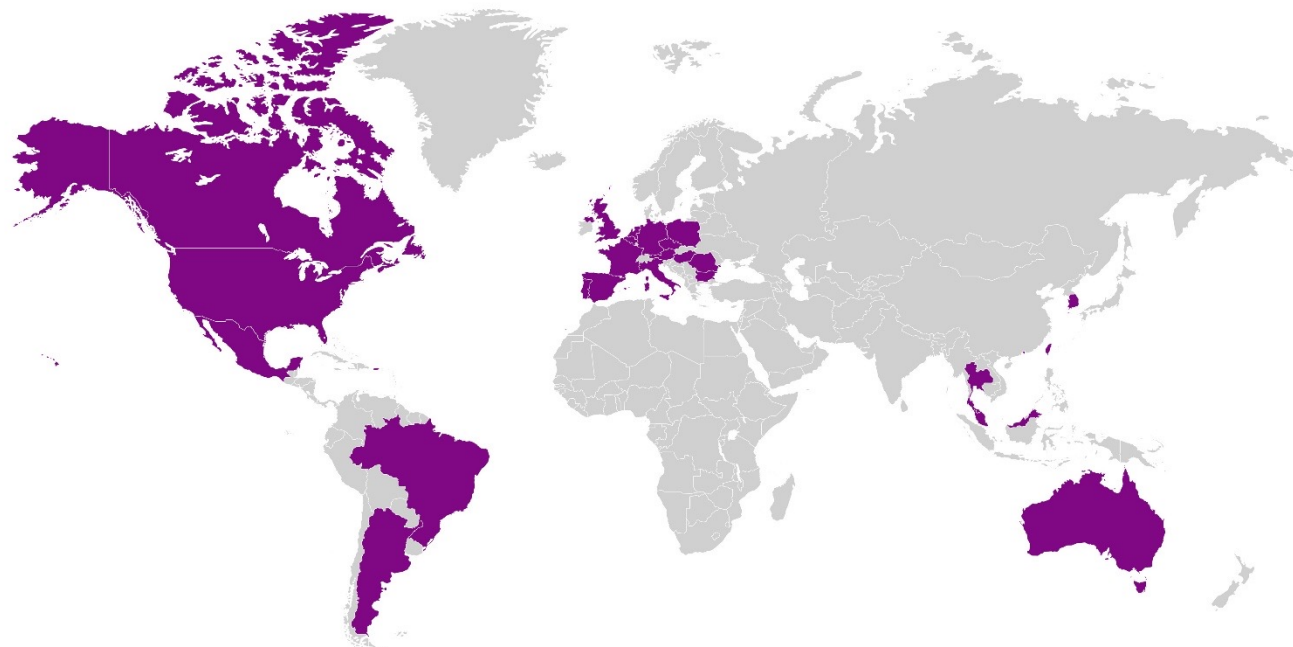
- OS in the *ESR1*-mut population
- OS in the *ESR1*-mut-nd population

Other secondary endpoints

- PFS (per local investigator) for *ESR1*-mut, *ESR1*-mut-nd, and all patients
- ORR, CBR, and DOR (per BIRC and local investigator) in *ESR1*-mut, *ESR1*-mut-nd, and all patients
- Safety and tolerability
- Pharmacokinetics
- Patient-reported outcomes

BIRC, blinded independent review committee; CBR, clinical benefit rate; DOR, duration of response; *ESR1*, estrogen receptor 1; *ESR1*-mut, *ESR1* mutation; *ESR1*-mut-nd, *ESR1* mutation not detected; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

GEOGRAPHIC FOOTPRINT OF OPERA-01



Enrollment began in November 2023.

References

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Disclosures

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Contact

For more information about the OPERA-01 trial, please visit the clinicaltrials.gov website or email OPERA-01@olema.com

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