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

OPERA-01 Breast Cancer Study

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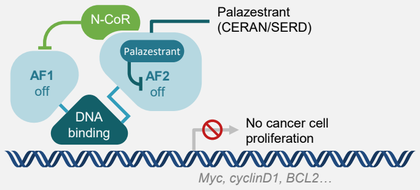
Background

- In estrogen receptor (ER)-positive, human epidermal growth factor receptor 2-negative, (HER2–) metastatic breast cancer (BC), adding a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor to endocrine therapy (ET) has improved outcomes and is the current standard-of-care treatment in the first-line setting.[1]
- ET resistance to first-line treatment develops in most patients, which is often attributed to acquired mutations in *ESR1*.[2] Limited data exist for ET-based treatment options after progression on prior ET and CDK4/6 inhibitors, and most patients will transition to chemotherapy for further treatment.
- Palazestrant (OP-1250) is a small molecule oral complete ER antagonist (CERAN) and selective ER degrader (SERD) that binds the ligand-binding domain of ER and completely blocks ER-driven transcriptional activity in both wild-type (*ESR1*-wt) and mutant (*ESR1*-mut) forms of ER.
- In preclinical studies, palazestrant demonstrated better tumor shrinkage in *ESR1*-wt and *ESR1*-mut models when compared to fulvestrant; it also showed efficacy in brain metastasis models.[3]

Palazestrant (OP-1250) Mechanism of Action

Palazestrant blocks AF1 and AF2 transcriptional activity, acting as a CERAN



AF, activation function; **CERAN**, complete estrogen receptor antagonist; **N-CoR**, nuclear receptor corepressor; **SERD**, selective estrogen receptor degrader.

- In early-phase trials, palazestrant was well tolerated, with favorable pharmacokinetics supporting once-daily dosing; it also showed antitumor activity and combinability with palbociclib[4] and ribociclib.[5]
- In a phase 2 monotherapy study in patients with heavily pretreated ER+/HER2– advanced BC, median progression-free survival (PFS) was 4.6 months for all patients and 5.6 months for *ESR1*-mutant patients; the clinical benefit rate (CBR) was 40% and 52%, respectively.[6]
  - In patients who received palazestrant as second- or third-line treatment, with or without prior chemotherapy, median PFS was 7.2 months for all patients and 7.3 months for *ESR1*-mutant patients,[6] which compares favorably to historical data in this patient population.[4,*]

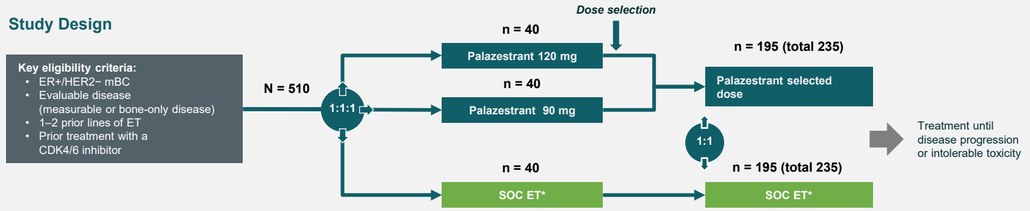
*This incorporates publicly available data that has not been independently verified and does not constitute a head-to-head comparison between palazestrant and any other available or investigational SERD.

OPERA-01: Study Design & Eligibility

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

- The study will compare the safety and efficacy of palazestrant to the standard-of-care options of fulvestrant or an aromatase inhibitor in women and men with BC whose disease has advanced on at least one ET in combination with a CDK4/6 inhibitor.
- The study consists of two parts: a three-arm dose selection part (part 1), followed by assessment of the selected dose of palazestrant versus standard of care (part 2).

Study Design



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

*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 recommended for premenopausal women and for men.

CDK, cyclin-dependent kinase; **ER+**, estrogen receptor-positive; ***ESR1***, estrogen receptor 1; **ET**, endocrine therapy; **GnRH**, gonadotropin-releasing hormone; **HER2−**, human epidermal growth factor receptor 2-negative; **mBC**, metastatic breast cancer; **mut-nd**, without detectable *ESR1* mutation; **SOC**, standard of care

Inclusion Criteria*:

- Adult female or male participants
- ER+/HER2- locally-advanced or metastatic BC that is not amenable to curative therapy
- Evaluable disease (measurable per RECIST v1.1 or bone-only)
- Previously received a CDK4/6 inhibitor in combination with ET in the advanced setting – one additional line of ET as a monotherapy will be allowed
- Eastern Cooperative Oncology Group performance status of 0 or 1
- Adequate hematologic, hepatic, and renal function
- Female participants can be pre-, peri-, or postmenopausal
- Male and pre- or perimenopausal female participants must be willing to take a gonadotropin-releasing hormone (luteinizing hormone-releasing hormone) agonist

Exclusion Criteria*:

- Symptomatic visceral disease, imminent organ failure, or any disease burden that makes the participant ineligible for ET
- Received prior chemotherapy in the advanced/metastatic setting
- Any contraindications to the selected standard-of-care ET in the local prescribing information
- Symptomatic central nervous system (CNS) metastases, carcinomatous meningitis, leptomeningeal disease, or a spinal cord compression that require immediate CNS-directed treatment
- Clinically significant comorbidities such as significant cardiac or cerebrovascular disease, or gastrointestinal disorders that could affect absorption of study treatment, and others
- Have received a prior elacestrant or experimental SERD

*For complete inclusion and exclusion criteria, visit: https://clinicaltrials.gov/study/NCT06016738

Endpoints

Primary endpoints

- PFS, as assessed by blinded independent review committee (BIRC), in the population with *ESR1* mutation (*ESR1*-mut)
- PFS, as assessed by BIRC, in the population without detectable *ESR1* mutation (*ESR1*-mut-nd)

Key secondary endpoints

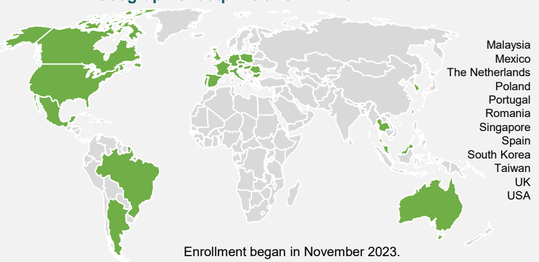
- Overall survival (OS) in the population with *ESR1* mutation
- OS in the population without detectable *ESR1* mutation

Other secondary endpoints

- PFS (per local investigator) for *ESR1*-mut, *ESR1*-mut-nd, and all patients
- Objective response rate, CBR, and duration of response (per BIRC and local investigator) in *ESR1*-mut, *ESR1*-mut-nd, and all patients
- Safety and tolerability
- Pharmacokinetics
- Patient-reported outcomes

Geographic footprint of OPERA-01

Argentina
Australia
Austria
Belgium
Brazil
Bulgaria
Canada
Czechia
France
Germany
Hong Kong
Hungary
Italy



Malaysia
Mexico
The Netherlands
Poland
Portugal
Romania
Singapore
Spain
South Korea
Taiwan
UK
USA

Enrollment began in November 2023.

References

1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer. V2.2023. **2.** Rasha F, et al. *Mol Cell Endocrinol*. 2021;532:111322. **3.** Hodges-Gallagher L, et al. Presented at SABCS. December 10−14, 2019. Abstract: P5-05-02. **4.** Chan A, et al. Presented at ESMO Breast Annual Congress. May 11−15, 2023. Abstract: 202P. **5.** Borges V, et al. Presented at SABCS. December 5−9, 2023. Abstract: 1580446. **6.** Lin NU, et al. Presented at ESMO Congress. October 20−24, 2023. Abstract: 382MO.

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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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