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

Abstract # TPS1135

OPERA-01 Breast Cancer Study

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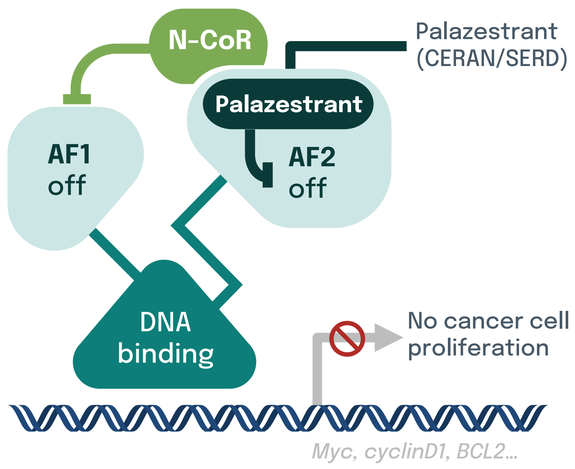
BACKGROUND

- In estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2-), metastatic breast cancer (mBC), adding a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) to endocrine therapy (ET) has improved outcomes and is the current standard-of-care (SOC) treatment in the first-line setting.[1]
- ET resistance to first-line treatment develops in most patients, which is often attributed to activating mutations in *ESR1*.[2] Limited options exist for treatment after progression on prior ET and CDK4/6i, and most patients will transition to chemotherapy.
- Palazestrant (OP-1250) is a small molecule oral complete ER antagonist (CERAN) and selective ER degrader (SERD) that binds to 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.[3] (Figure 1)
- 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]

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

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*-mut 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*-mut patients,[6] which compares favorably to available treatment options in this patient population.[4,*]

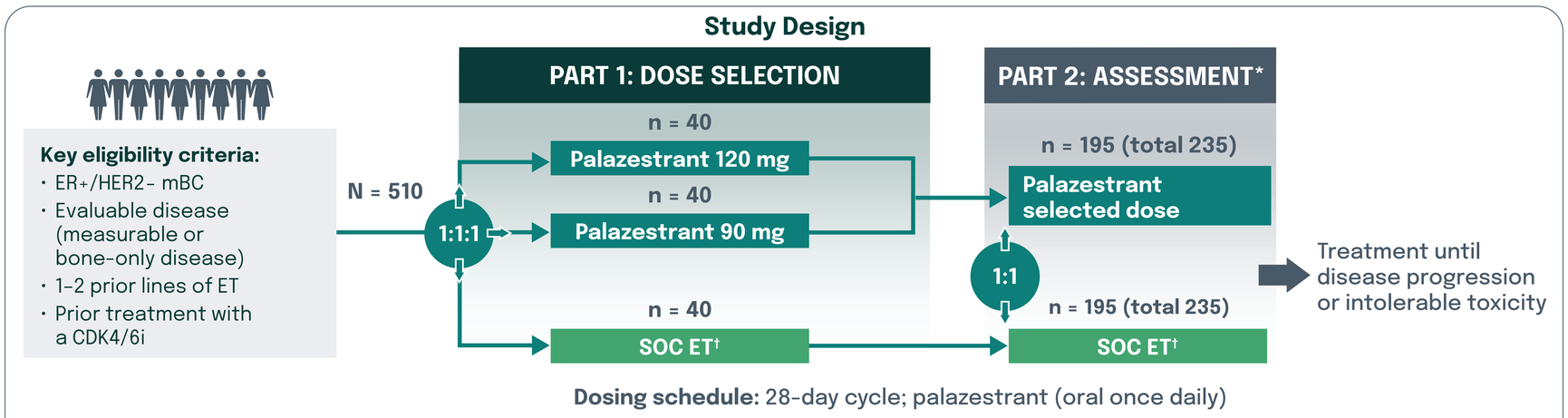
*This incorporates publicly available data that have not been independently verified and does not constitute a head-to-head comparison between palazestrant and any other available or investigational SERD.

OPERA-01: STUDY DESIGN & ELIGIBILITY

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

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

OPERA-01 TRIAL SCHEMA



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

*The dose for Part 2 will be selected based on safety, efficacy, pharmacokinetics, and health-related patient-reported outcomes in Part 1.
†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.

CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; **ER+,** estrogen receptor-positive; **ET,** endocrine therapy; **GnRH,** gonadotropin-releasing hormone; **HER2-,** human epidermal growth factor receptor 2-negative; **IM,** intramuscular; **mBC,** metastatic breast cancer; **SOC,** standard-of-care.

Key eligibility criteria

Inclusion Criteria:

- Adult female or male patients
- 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 and progressed on a CDK4/6i in combination with ET in the advanced setting
  - duration of the most recent prior ET must be at least 6 months
  - one additional line of ET will be allowed
- Eastern Cooperative Oncology Group 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 GnRH (luteinizing hormone-releasing hormone) agonist

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, and others
- 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

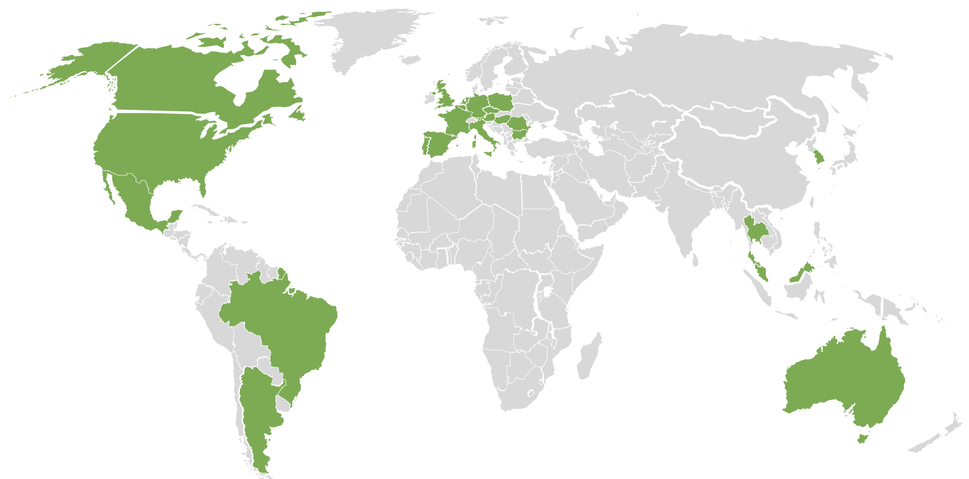
- OS in the *ESR1*-mut population
- OS in the *ESR1*-mut-nd population

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



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Austria	Czechia	Italy	Portugal	Thailand
Belgium	France	Malaysia	Romania	UK
Brazil	Germany	Mexico	Spain	USA

Enrollment began in November 2023.

References

1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer. V2.2024. **2.** Rasha F, et al. *Mol Cell Endocrinol.* 2021;532:111322. **3.** Parisian AD, et al. *Mol Cancer Ther.* 2024;23:285-300. **4.** Chan A, et al. Presented at ESMO Breast Annual Congress. May 11-15, 2023. Abstract: 202P. **5.** Borges VF, et al. Presented at ESMO Breast Annual Congress. May 15-17, 2024. Abstract: 212P. **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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