OPERA-02: A phase 3, randomized, double-blind, active-controlled study of palazestrant with ribociclib *vs* letrozole with ribociclib for the first-line treatment of ER+, HER2– advanced breast cancer

Poster # 261b

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BACKGROUND

- The current standard first-line therapy for estrogen receptor-positive (ER+), human epidermal growth factor-negative (HER2–) advanced breast cancer (ABC) is an aromatase inhibitor (AI) in combination with a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i).[1]
- Ribociclib is the only agent that, when combined with an AI, has demonstrated improvements in both progression-free survival (PFS) and overall survival (OS) in this population.[2]
- Despite these advances, most patients ultimately develop resistance to AI + CDK4/6i therapy. A key mechanism of endocrine resistance involves estrogen receptor 1 (*ESR1*) gene mutations, which affect the ligand-binding domain of estrogen receptor alpha (ERα) and lead to estrogen-independent constitutive activation.[3]
- AIs can promote the development of *ESR1* mutations.[4] Therefore, therapeutic approaches that inhibit both wildtype and mutant ERα in the first-line setting may help maintain endocrine sensitivity, delay resistance, and improve long-term clinical outcomes.
- Palazestrant (OP-1250) is a novel, investigational oral complete estrogen receptor antagonist (CERAN) and selective estrogen receptor degrader (SERD) that effectively inhibits wildtype and *ESR1*-mutant ERα signaling in ER+, HER2– ABC models.[5,6]

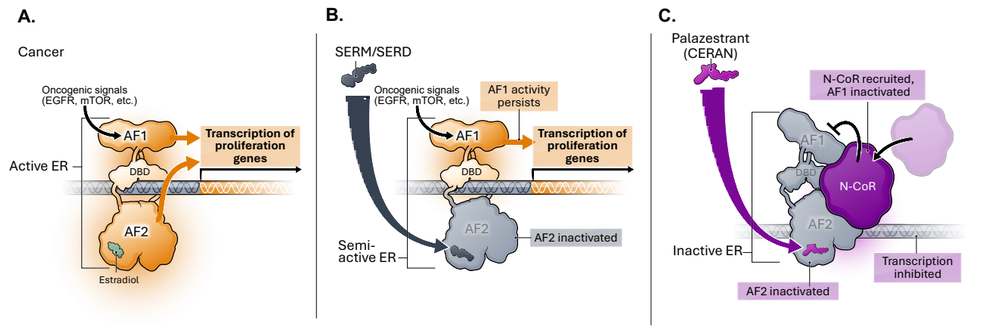


Figure 1. Palazestrant mechanism of action.

A. ERα regulates expression of cell survival and proliferation genes. Binding of estrogen stimulates two activation functions (AF1 and AF2) to induce conformational changes promoting transcription and signaling. **B.** SERMs (i.e., tamoxifen) competitively inhibit estrogen binding to block AF2 mediated transcription but allow agonist signaling through AF1 via other signaling pathways.[7] **C.** Palazestrant, a CERAN and SERD, completely inhibits both AF2 and AF1, triggering proteasomal degradation of inactive ERα, regardless of mutation status. AF1 inhibition by palazestrant occurs through recruitment of ER corepressor proteins including N-CoR.[8-10]

CERAN, complete estrogen receptor antagonist; **DBD**, DNA binding domain; **EGFR**, epidermal growth factor receptor; **ER**, estrogen receptor; **ERα,** estrogen receptor alpha; **mTOR**, mammalian target of rapamycin; **N-CoR**, nuclear receptor corepressor; **SERD,** selective estrogen receptor degrader; **SERM**, selective estrogen receptor modulator.

- In the early phase clinical study, combination of palazestrant with ribociclib had a tolerable safety profile, favorable pharmacokinetics without clinically meaningful drug-drug interactions, and encouraging efficacy.[11] The safety of the combination of palazestrant and ribociclib was consistent with the known safety profiles of each drug.[12] No increase in incidence or severity of neutropenia compared to the combination of ribociclib with letrozole was observed.[13]
- In the 90-mg palazestrant dose cohort of the early phase OP-1250-003 study, the median PFS was not reached. In the 120-mg palazestrant dose cohort, median PFS was 15.5 months in all patients, 12.2 months with prior CDK4/6i, 9.2 months with *ESR1*-wildtype with prior CDK4/6i, and 13.8 months for *ESR1*-mutant with prior CDK4/6i-treated ABC.[13]
- This data supports the OPERA-02 study evaluating 90 mg once-daily palazestrant in combination with 600 mg ribociclib for the first-line treatment of ER+, HER2– ABC.

OPERA-02: STUDY DESIGN & ELIGIBILITY

Key inclusion criteria:

- ER+/HER2– ABC (endocrine sensitive)
- Any menopausal status
- Evaluable disease (measurable or non-measurable)
- No prior systemic therapy for ABC
- No disease recurrence during or within 12 months of completing adjuvant therapy

N ≈ 1000

1:1

90 mg QD palazestrant + 600 mg ribociclib* + letrozole matching placebo — n ≈ 500

2.5 mg letrozole + ribociclib* + palazestrant matching placebo — n ≈ 500

*600 mg ribociclib (3 weeks on/1 week off)

Stratification:

- Menopausal status: post *vs* pre- or peri-/male
- Visceral metastasis: yes *vs* no
- De novo metastatic disease *vs* recurrent disease after adjuvant ET
- Geographical region: US, Canada and Australia *vs* Europe *vs* Other

ET, Endocrine Therapy; **QD,** once daily.

ENDPOINTS

Primary endpoint

- PFS, as assessed by local investigator

Key secondary endpoint

- OS

Other secondary endpoints

- PFS (per BIRC)
- ORR, CBR, and DOR (per local investigator and BIRC)
- PFS2
- Safety and tolerability
- PK
- Patient-reported outcomes

BIRC, blinded independent review committee; **CBR,** clinical benefit rate; **DOR**, duration of response; **ORR,** objective response rate; **OS,** overall survival; **PFS,** progression-free survival; **PFS2**, progression-free survival 2; **PK,** Pharmacokinetics.

Key Inclusion Criteria*:

- Adult female or male participants
- ER+, HER2– advanced breast cancer (locally advanced or metastatic breast cancer) that is not amenable to curative therapy
- Newly diagnosed advanced breast cancer or disease recurrence occurring after 12 months of completing adjuvant endocrine therapy with or without CDK4/6 inhibitor
- Evaluable disease (measurable disease or evaluable bone disease)
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
- Adequate hematologic, hepatic, and renal functions
- Female participants can be pre-, peri-, or post-menopausal
- Male and pre- or peri-menopausal female participants must be willing to take a gonadotropin-releasing hormone (GnRH) or luteinizing hormone-releasing hormone (LHRH) agonist

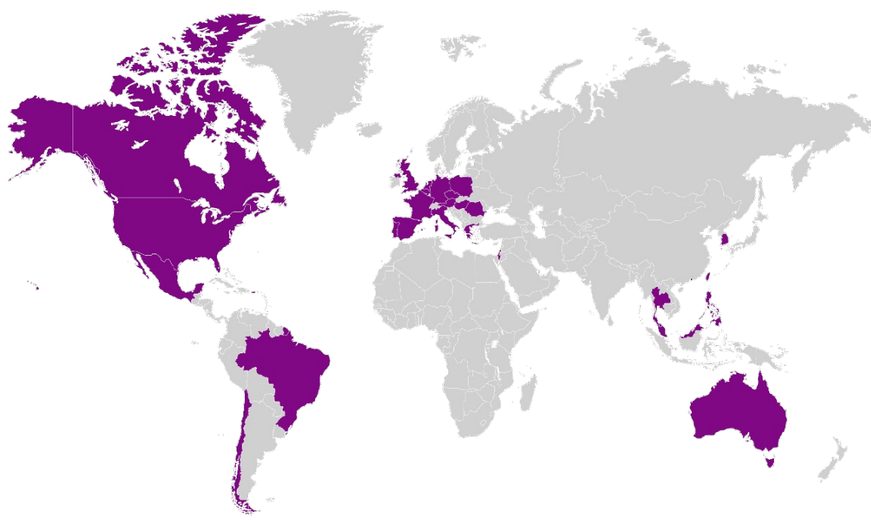
***For complete inclusion and exclusion criteria, visit: https://clinicaltrials.gov/study/NCT07085767**

Key Exclusion Criteria*:

- Disease recurrence during or within 12 months of completing adjuvant endocrine therapy
- Prior treatment with a SERD or any investigational endocrine therapy
- Patients who are ineligible to begin treatment with ribociclib or letrozole per local prescribing information
- Active or symptomatic central nervous system metastases, carcinomatous meningitis, leptomeningeal disease, or a spinal cord compression that require immediate treatment
- Clinically significant comorbidities such as cerebrovascular disease, pulmonary disease, psychiatric 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

***For complete inclusion and exclusion criteria, visit: https://clinicaltrials.gov/study/NCT07085767**

GEOGRAPHIC FOOTPRINT OF OPERA-02



Australia, Austria, Belgium, Brazil, Canada, Chile, Czechia, France, Germany, Greece, Hong Kong, Hungary, Israel, Italy, Malaysia, Mexico, The Netherlands, The Philippines, Poland, Portugal, Romania, South Korea, Spain, Taiwan, Thailand, UK, USA

Enrollment began in November 2025.

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Contact

For more information about the OPERA-02 trial, please visit the clinicaltrials.gov website or email **OPERA-02@olema.com**

ClinicalTrials.gov ID: NCT07085767

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