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 # PS5-12-18

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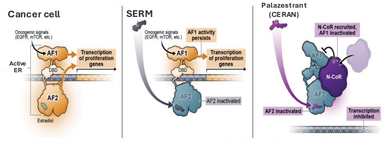
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OPERA-02 Breast Cancer Study

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]
- Because AIs can promote the development of *ESR1* mutations,[4] therapeutic approaches that inhibit both wild-type 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 wild-type and *ESR1*-mutant ERα signaling in ER+, HER2– ABC models.[5,6]

Figure 1: Mechanism of Action of Palazestrant (OP-1250)[5]

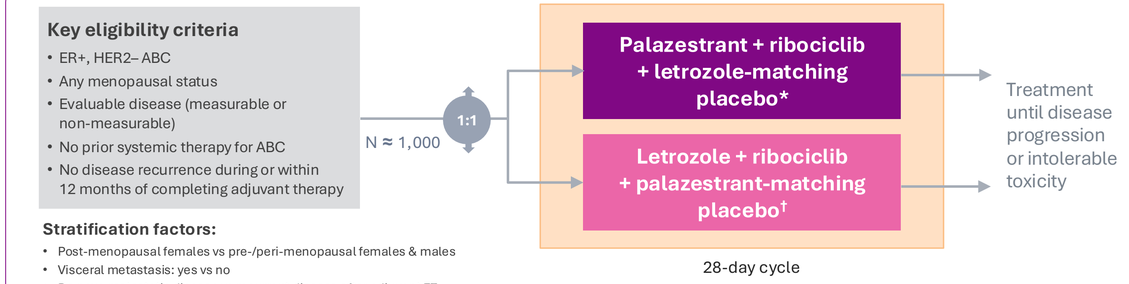


AF, activation function; **CERAN**, complete estrogen receptor antagonist; **DBD**, DNA binding domain, **EGFR**, epidermal growth factor receptor, **ER**, estrogen receptor; **mTOR**, mammalian target of rapamycin; **N-CoR**, nuclear receptor corepressor; **SERM**, selective estrogen receptor modulator.

- In the early phase clinical study, combination of palazestrant with ribociclib had a tolerable safety profile, favorable pharmacokinetics without clinically meaningful drug-drug interactions with ribociclib, and encouraging efficacy.[7] When combined, palazestrant and ribociclib safety was consistent with the known safety profiles of each drug.[8] No increase in incidence or severity of neutropenia compared to the combination of ribociclib with letrozole was observed.[9]
- 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 mos in all patients, 12.2 mos with prior CDK4/6i, 9.2 mos with *ESR1*-wt with prior CDK4/6i, and 13.8 mos for *ESR1*-mut with prior CDK4/6i-treated ABC.[9]
- 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

OPERA-02: Phase 3, randomized, double-blind study of palazestrant with ribociclib vs letrozole with ribociclib for ER+, HER2– ABC



*Palazestrant 90 mg QD and letrozole-matching placebo QD on days 1-28; ribociclib 600 mg QD on days 1-21. †Letrozole 2.5 mg QD and palazestrant-matching placebo QD on days 1-28; ribociclib 600 mg QD on days 1-21.
ABC, advanced breast cancer; **ER+**, estrogen receptor positive; **ET**, endocrine therapy; **HER2–**, human epidermal growth factor receptor 2 negative; **QD**, once daily.

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
- Evaluable disease (measurable disease or evaluable bone disease)
- 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

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
- Contraindication to ribociclib or letrozole
- 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

ENDPOINTS

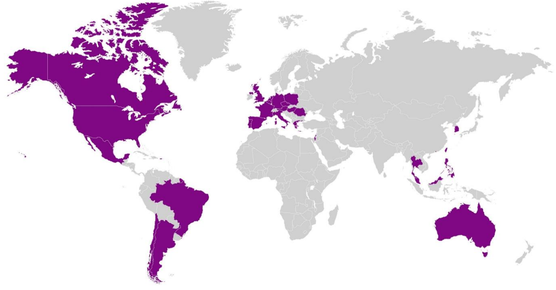
Primary endpoint
- PFS, as assessed by local investigator

Key secondary endpoints
- OS

Other secondary endpoints
- PFS (per BIRC)
- ORR, CBR, and DOR (per local investigator and BIRC)
- PFS2
- Safety and tolerability
- Pharmacokinetics
- 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.

GEOGRAPHIC FOOTPRINT OF OPERA-02



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

Enrollment is ongoing

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Disclosures
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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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