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 CDK4/6 inhibitor therapy

Background
- In estrogen receptor (ER)-positive, human epidermal growth factor receptor 2-negative (HER2−) metastatic breast cancer (mBC), 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.
- ET resistance to first-line treatment develops in most patients, which is often attributed to acquired mutations in ESR1. 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 transcribed 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 compared to fulvestrant; it also showed efficacy in brain metastasis models.

Mechanism of Action
Palazestrant (OP-1250) acting as a CERAN

Inclusion Criteria*
- Adult female or male participants
- ER+ /HER2− locally-advanced or metastatic BC that is not amenable to curative therapy
- Evaluable disease (measurable according to 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 or as monotherapy
- Eastern Cooperative Oncology Group performance status of 0 or 1
- Evaluable disease (measurable or bone-only disease)

Exclusion Criteria*
- Any contraindications to the selected standard-of-care ET in the population
- Symptomatic visceral disease, imminent organ failure, or any disease burden that makes the participant ineligible for ET

Endpoints
Primary endpoints
- PFS, as assessed by blinded independent review committee (BIRC), in the population with ESR1 mutation (ESR1-mut-mBC)
- PFS, as assessed by BIRC, in the population without detectable ESR1 mutation (ESR1-wt-mBC)

Key secondary endpoints
- Overall survival (OS) in the population with ESR1 mutation
t- OS in the population without detectable ESR1 mutation

Other endpoints
- PFS (per local investigator) for ESR1-mut-mBC, and all patients
- Objective response rate, CBR, and duration of response (per BIRC and local investigator) in ESR1-mut-mBC, eth and all patients
- Safety and tolerability
- Pharmacokinetics

Patient-reported outcomes

Acknowledgements

References

Disclosure

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

Fig. 1. Study design and eligibility

In a phase 2/3 Mayo Clinic Endocrinology Pattern of Care Study (ESR1-mut vs SOC ET* in 550 patients with ESR1+) treatment until disease progression or unacceptable toxicity

Inclusion Criteria*
- Adult female or male participants
- ER+/HER2− locally-advanced or metastatic BC that is not amenable to curative therapy
- Evaluable disease (measurable according to 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 or as monotherapy
- 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 peri-menopausal female participants must be willing to use 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, leptomaengal 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 compromise the ability of study and treatment, and others
- Have received a prior erasest or experimental SERD

*For complete inclusion and exclusion criteria, visit: https://clinicaltrials.gov/ct2/show/NCT04017538

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The geographic footprint of OPERA-01 is broad and includes countries and regions from around the world, including the United States, Europe, Asia, and Australia, as well as regions in Latin America and the Middle East. This indicates the global reach and diversity of the trial participants.