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OPERA-01: a phase III study of palazestrant for ER+, HER2– advanced breast cancer after CDK4/6 inhibitor therapy

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ABSTRACT

Endocrine therapy (ET) resistance is a major concern when treating estrogen receptor-positive (ER+) human epidermal growth factor receptor 2-negative (HER2–) breast cancer. A combination of cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) and ET is the current first-line standard of care (SOC) for patients with ER+, HER2– advanced breast cancer. Despite the benefits of ET plus a CDK4/6i, disease progression due to endocrine resistance remains a significant challenge. More effective ETs that can overcome resistance are needed to improve clinical outcomes and maintain quality of life by delaying chemotherapy. Palazestrant is a novel oral, complete estrogen receptor antagonist (CERAN) and selective estrogen receptor degrader (SERD) that blocks both transcriptional activation function domains, AF1 and AF2, resulting in complete inhibition of ER-driven transcription, regardless of estrogen receptor 1 (*ESR1*) mutation status. As monotherapy, palazestrant showed tolerable safety, favorable pharmacokinetics, and antitumor efficacy in heavily pretreated patients during phase I/II studies. OPERA-01 (NCT06016738) is a phase III study designed to evaluate the safety and efficacy of palazestrant monotherapy compared to SOC ET in patients with ER+, HER2– locally advanced or metastatic breast cancer, regardless of *ESR1* mutation status, whose disease advanced following treatment with at least one ET in combination with a CDK4/6i.

Clinical Trial Registration: Clinicaltrials.gov NCT06016738. Registered 17 August 2023.

PLAIN LANGUAGE SUMMARY

The most common type of breast cancer (BC) is estrogen receptor-positive (ER+; responds to estrogen) and human epidermal growth factor receptor 2-negative (HER2–; does not overproduce HER2 protein). Because estrogen promotes the growth of ER+, HER2– BCs, endocrine therapy (ET) that reduces the amount or the effect of estrogen is typically used to treat this BC subtype. ET is often combined with another class of medications called cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) to treat ER+, HER2– advanced BC. Unfortunately, this combination eventually stops working due to mutations that develop in genes, including the estrogen receptor gene (*ESR1*), which allow cancers to grow without estrogen. Patients whose tumors develop mutations must then switch to a different ET to control their disease. Thus, there is a need for new ETs that are safe and can overcome ET resistance, thereby helping tumors remain under control which allows patients to maintain their quality of life by delaying the need for chemotherapy. Palazestrant is a new oral ET taken once daily that may be effective against tumors with or without a mutation in *ESR1*. Clinical studies showed that palazestrant was safe in people with ER+, HER2– BCs. To better understand how well palazestrant works, the ongoing OPERA-01 study is comparing the effects of palazestrant to standard-of-care ETs in patients with ER+, HER2– locally advanced or metastatic BC, with or without a mutation in *ESR1*, whose cancer is no longer under control after treatment with at least one ET in combination with a CDK4/6i.

TWEETABLE ABSTRACT

OPERA-01 is a phase III clinical trial comparing palazestrant to standard-of-care endocrine therapy for ER+, HER2– advanced breast cancer after endocrine and CDK4/6 inhibitor therapy. Enrolling at multiple sites worldwide. (NCT06016738)

ARTICLE HISTORY
Received 1 August 2025
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KEYWORDS
CERAN; SERD; ER+; HER2– locally advanced or metastatic breast cancer; endocrine therapy; palazestrant; *ESR1* mutation

1. Introduction

Breast cancer is the most common cancer in women and the leading cause of cancer deaths globally. In 2022, an estimated 2.3 million women were diagnosed with breast cancer worldwide, and 666,000 succumbed to their disease [1]. The most common subtype of breast cancer isestrogen receptor-positive (ER+),

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Article highlights

BACKGROUND AND RATIONALE

- A combination of cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) and endocrine therapy (ET) is the current first-line standard of care (SOC) for patients with estrogen receptor-positive (ER+), human epidermal growth factor 2-negative (HER2–) advanced breast cancer (ABC).
- Endocrine resistance remains a significant challenge and eventually develops in most patients, commonly due to mutations in the estrogen receptor 1 gene (*ESR1).*
- There is an unmet clinical need for effective ETs that can overcome and delay resistance and improve outcomes in patients with and without *ESR1* mutations.

PALAZESTRANT FOR TREATMENT OF ER+, HER2– LOCALLY ADVANCED OR METASTATIC BREAST CANCER

- Palazestrant is a novel oral, complete estrogen receptor antagonist (CERAN) and selective estrogen receptor degrader (SERD) that blocks both transcriptional activation function (AF) domains, AF1 and AF2, resulting in complete inhibition of ER-driven transcription regardless of *ESR1* mutation status.
- Palazestrant has demonstrated activity in both *ESR1*-wild type (*ESR1*-wt) and *ESR1*-mutated (*ESR1*-mut) preclinical models as well as central nervous system (CNS) penetration and demonstrated antitumor activity in brain metastasis models.
- In a phase I/II study, palazestrant monotherapy showed favorable tolerability, encouraging antitumor activity that may counteract endocrine resistance due to *ESR1* mutations, suppress the emergence of *ESR1* mutations, and demonstrate a pharmacokinetic profile supportive of once-daily oral dosing in patients with ER+, HER2– ABC.

OPERA-01 STUDY DESIGN

- OPERA-01 (NCT06016738) is an ongoing phase III study designed to evaluate the safety and efficacy of palazestrant monotherapy compared to SOC ET in patients with ER+, HER2– locally advanced or metastatic breast cancer, regardless of *ESR1* mutation status, whose disease advanced following treatment with at least one ET in combination with a CDK4/6i.
- Approximately 510 men or women (including 470 in the primary analysis) with ER+, HER2– locally advanced or metastatic breast cancer whose disease advanced following treatment with at least one ET in combination with a CDK4/6i will be enrolled.
- In Part 1, the dose-selection portion of the study, eligible patients were randomized 1:1:1 to receive once-daily oral palazestrant at a dose of 90 mg or 120 mg or investigator's choice of SOC ET (fulvestrant or an AI).
- In Part 2, eligible patients will be randomized 1:1 to receive once-daily oral palazestrant at the selected dose in Part 1 (i.e., 90 mg) or the investigator's choice of SOC ET.
- The dual primary endpoint of the overall study is blinded independent committee review (BICR)-assessed progression-free survival (PFS), in patients with *ESR1*-mut tumors and those with no mutation detected (*ESR1*-mut-nd), to be assessed separately.
- Additional ongoing studies show encouraging safety and preliminary efficacy with palazestrant in combination with the full dose of ribociclib, providing justification for future evaluation of combination treatment.

CONCLUSION

- This study will provide insights into the safety and efficacy of palazestrant compared to SOC ET in patients with pretreated ER+, HER2– ABC, regardless of the *ESR1* mutation status, potentially leading to a new and effective treatment option for this patient population.

human epidermal growth factor receptor 2-negative (HER2–) cancer, accounting for approximately 70% of all cases [2–6].

Patients with ER+ breast cancer typically receive endocrine therapy (ET) that acts to suppress ER signaling by one of the three primary mechanisms [2,7,8]. Aromatase inhibitors (AIs) block estradiol synthesis, selective estrogen receptor modulators (SERMs) antagonize the effects of estradiol via competitive ER binding, and selective estrogen receptor degraders (SERDs) fully antagonize the ER and target it for degradation [7,8]. However, each ET mechanism has drawbacks that impact therapeutic utilities such as development of resistance mutations in response to AIs and partial agonist activity of SERM in other organs, including the uterus [8,9]. SERDs have the potential to overcome some of these challenges, but the only SERD currently approved as monotherapy and combination therapy, fulvestrant, has challenging pharmacokinetic properties that necessitate intramuscular administration, limiting the volume of the administered dose and thereby its dose-dependent efficacy [10–12]. SERDs with improved pharmacological properties, including oral availability, are needed to overcome these limitations to provide more effective treatment options in this disease space.

Although only 5% of patients with ER+, HER2– breast cancer have metastases at diagnosis, approximately 30% of patients treated with ET for early-stage disease eventually develop metastatic disease [3,4,13–15]. The combination of a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) with ET is the recommended first-line treatment for patients with ER+, HER– advanced breast cancer (ABC) [16–18]. For those who progress on CDK4/6i and ET, international guidelines advise treatment with sequential endocrine therapy-based options, potentially delaying the need to transition to chemotherapy or antibody–drug conjugates that are recommended for patients who develop endocrine resistance [14,16–18]. These later lines of therapy are associated with increased toxicity that can negatively impact patient quality of life [19–21].

Endocrine resistance commonly occurs due to mutation of estrogen receptor 1 (*ESR1)*, the gene encoding estrogen receptor alpha (ERα) [22,23]. While *ESR1* mutations are infrequent in treatment-naïve breast cancer, up to ~50% of patients receiving AI therapy have been reported to develop activating *ESR1* mutations that drive constitutive estrogen-independent receptor activation [9,23]. As resistance to ET develops, the therapeutic benefit generally decreases with each subsequent line of treatment [24,25]. Given the high prevalence of patients with resistance to ET, therapies with activity in patients with *ESR1*-activating mutations are an area of active development [23,26–30]. However, recent reports indicate that the clinical benefit in ER+, HER2– ABC may be limited to patients with *ESR1*-mutated (*ESR1*-mut) tumors, rather than the entire patient population: trials investigating the efficacy of the PROteolysis Targeting Chimera ER degrader (PROTAC), vepdegestrant, and the SERD, imlunestrant, showed progression-free survival (PFS) benefits specific to patients harboring *ESR1* mutations [28,29]. Similarly, the SERD elacestrant showed a more favorable risk–benefit ratio in patients with *ESR1* mutations and was recently approved for postmenopausal women or adult men with ER+, HER2– *ESR1*-mut advanced or metastatic breast cancer with disease progression following at least one prior line of ET [30,31].

While treatment with ET and CDK4/6i provides benefit to patients with ER+, HER2– ABC, disease progression due to acquired resistance to the combination remains a challenge [32–35]. There is an unmet need for therapies that can overcome or suppress the development of resistance and are effective regardless of *ESR1* mutation status. Targeting the ER with ETs that have more potent ER antagonism may prove to be an effective therapeutic strategy to improve outcomes and patient experience by delaying the transition to more toxic therapies.

1.1. Palazestrant for treatment of ER+, HER2– locally advanced or metastatic breast cancer

Palazestrant is a next-generation, orally bioavailable complete estrogen receptor antagonist (CERAN) and SERD with potent activity targeting the ER [36,37]. Palazestrant blocks both transcriptional activation function (AF) domains, AF1 and AF2 (Figure 1), resulting in a complete inhibition of ER-driven transcription regardless of *ESR1* mutation status [36]. Palazestrant promotes ER degradation at levels similar to that of fulvestrant and greater than that of elacestrant [36]. However, the presence of residual ER protein has been detected in vitro with these treatments [36], suggesting that additional ER antagonist activity may be required to fully abrogate ER function. Importantly, palazestrant showed high-affinity ER binding and pure ER antagonism by inhibiting the activity of both AF1 and AF2 domains [36]. Therefore, palazestrant demonstrates robust CERAN activity that completely blocks ER-induced transcription, ensuring full inhibition of any residually available ER remaining from its SERD activity.

Preclinical studies demonstrated that palazestrant exhibits potent antitumor activity in *ESR1*-wild-type (*ESR1*-wt) and *ESR1*-mut models. In xenograft breast cancer models, palazestrant induced greater shrinkage of both *ESR1*-wt and HCI-013 $ESR1^{Y537S}$ tumors compared to fulvestrant with a more favorable pharmacokinetic profile, including oral bioavailability. Palazestrant also showed robust brain penetrance with brain/plasma ratios >1 and decreased intracranial tumoral growth in ST941 $ESR1^{Y537S}$ brain-metastasis models. Compared to elacestrant, palazestrant exhibited better antitumor activity at a fraction of the dose in the ST941 $ESR1^{Y537S}$ breast cancer model and resulted in greater tumor volume reduction compared to both fulvestrant and elacestrant [36].

Based on these preclinical data, the first-in-human, open-label, phase I/II OP-1250–001 study (NCT04505826) evaluated the safety and efficacy of palazestrant in patients with previously treated ER+, HER2– locally advanced or metastatic breast cancer [27,40]. Single-agent palazestrant was well tolerated through dose escalation at doses up to 300 mg/day. There were no dose-limiting toxicities, and the maximum tolerated dose was not reached; palazestrant 120 mg/day was determined as the recommended phase II dose (RP2D). Of the 86 patients treated at RP2D, 97% had received prior CDK4/6i, 76% had received ≥2 prior lines of systemic therapy in the advanced setting (median 2; range 1–6), and 48% (36/75) harbored baseline-activating *ESR1* mutations. The most common all-grade treatment-related adverse events (TRAEs) were nausea (55%), vomiting (24%), and fatigue (20%). Most TRAEs were grade 1–2 in severity. Grade 3 TRAEs were reported in 10 (11.6%) patients, most commonly nausea and neutropenia (n = 3 each, 3.5%), and vomiting and fatigue (n = 2 each, 2.3%). Five (5.8%) patients experienced grade 4 neutropenia that was resolved with dose interruptions, reductions, colony-stimulating factors, or discontinuation (n = 3). Discontinuation due to TRAEs occurred in ≤6% of patients. The incidence of bradycardia and photopsia observed was relatively low (9% and 5%, respectively) [27,41,42]; all events were grade 1 and did not lead to dose modifications, interruptions, or discontinuations [27].

Antitumor activity was observed in patients regardless of the *ESR1* mutation status, suggesting that palazestrant counteracts endocrine resistance driven by *ESR1* mutations. The

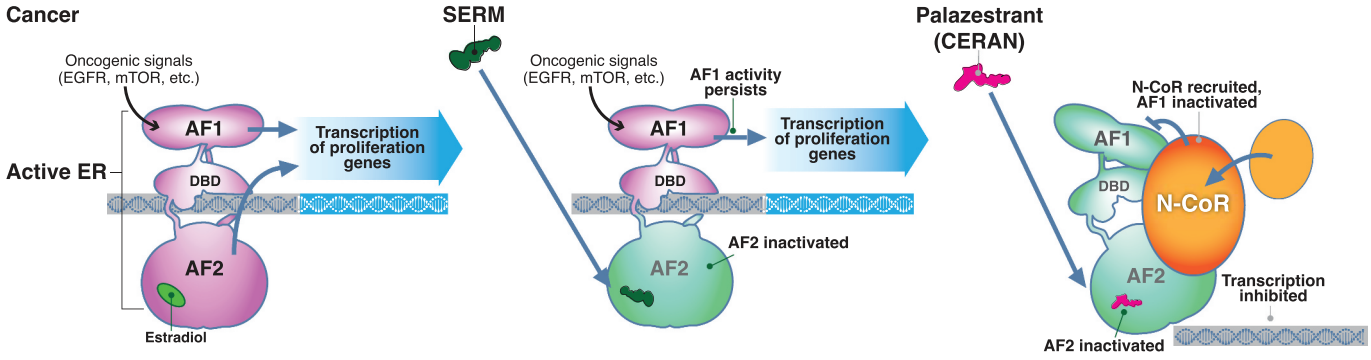


Figure 1. Palazestrant mechanism of action. The ER is a nuclear receptor that functions as a ligand-activated transcription factor to regulate expression of genes involved in survival and proliferation. Binding of estrogen to ERα stimulates two activation function (AF) domains, AF-1 and AF-2, inducing conformational changes in AF-2 that modulate interactions with regulatory proteins to promote transcription and signaling. Selective estrogen receptor modulators (SERMs), such as tamoxifen, competitively block estrogen binding to inhibit AF-2-driven transcription but allow agonist signaling through AF-1 via other signaling pathways such as mTOR, PI3K, and MAPK [23]. Palazestrant is both a CERAN and a SERD that competes with estrogen and inhibits activities of ERα activation function (AF) domains AF-2 and AF-1. Palazestrant completely blocks ER-driven transcriptional activity, triggering subsequent proteasomal degradation of the inactive ER for both wild-type and mutated ERα [36]. While the mechanism of AF-1 inhibition by CERANs such as palazestrant has not been determined, inhibitory activity may occur through recruitment of ER corepressor proteins such as N-CoR [38,39].

Abbreviations: AF, activation function; 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.

median PFS (mPFS) was 4.8 months (95% confidence interval [CI]: 3.5–7.1) in all patients and 5.6 months (95% CI: 4.8–not estimable [NE]) among patients with tumors harboring *ESR1* mutations. The clinical benefit rate (CBR) was 46% for all patients and 59% among patients with *ESR1*-mut disease [27]. In an analysis of 49 patients who received palazestrant as second- or third-line therapy, the mPFS was 7.2 months in all patients and 7.3 months for patients with *ESR1*-mut tumors (n = 23), demonstrating that palazestrant has promising clinical activity compared to historical data in heavily pretreated patients who have tumors with or without *ESR1* mutations [28,30,43]. Biomarker analysis showed that palazestrant led to a decrease in the number of *ESR1*-variant mutations that are associated with endocrine resistance, suggesting that palazestrant has activity across clinically relevant *ESR1* variants. These findings provide a rationale for the investigation of the safety and efficacy of palazestrant in patients with pretreated ER+, HER2– locally advanced or metastatic breast cancer, regardless of the *ESR1* mutation status, given the need for novel, effective treatment options for this patient population.

1.2. OPERA-01 rationale & study design

Based on the tolerability and promising efficacy of palazestrant demonstrated in early-phase studies, OPERA-01 (NCT06016738) was designed to evaluate the safety and efficacy of palazestrant monotherapy compared to standard-of-care (SOC) ET (fulvestrant, anastrozole, letrozole, or exemestane) in patients with ER+, HER2– locally advanced or metastatic breast cancer who have relapsed or progressed on 1–2 prior lines of ET, including a CDK4/6i [44].

2. Methods

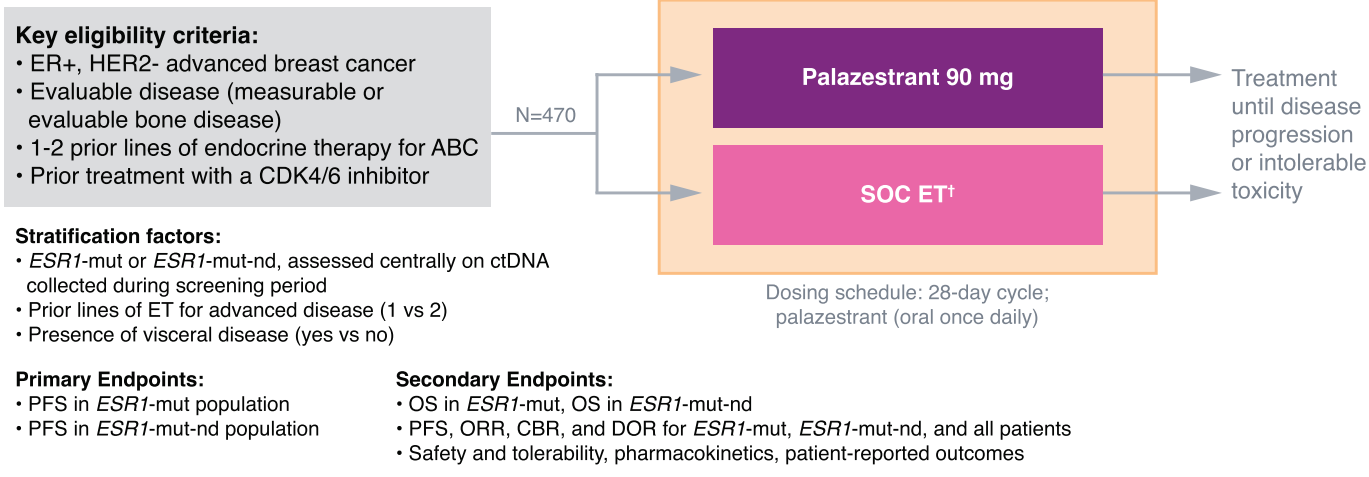
2.1. Overview

The OPERA-01 study is a global phase III randomized, open-label, active-controlled study, consisting of two parts (Figure 2). In Part 1, the dose-selection portion of the study, eligible participants were randomized 1:1:1 to receive oral palazestrant at a dose of 90 mg or 120 mg once daily (QD) or investigator's choice of SOC ET [fulvestrant 500 mg D1 of each cycle and D15 of cycle 1 or AI (letrozole 2.5 mg QD, anastrozole 1 mg QD, or exemestane 2.5 mg QD)]. Fulvestrant was recommended to patients who have not previously received fulvestrant. The Independent Data Monitoring Committee recommended a 90-mg palazestrant QD dose based on the available safety, efficacy, patient-reported outcomes, and pharmacokinetic data from participants treated in Part 1. In Part 2, participants are randomized at a 1:1 ratio to receive once-daily oral palazestrant (90 mg QD) or the investigator's choice of SOC ET. All treatments are administered in 28-day cycles and continue until confirmed radiographic disease progression, intolerable toxicity, continuous dose-interruption >28 days, investigator or participant decision, or initiation of a non-protocol anti-cancer therapy. This study is sponsored by Olema Oncology.

2.2. Study design

2.2.1. Eligibility criteria

Male and female participants aged 18 years or older are eligible for enrollment in the OPERA-01 study if they have a confirmed diagnosis of inoperable locally advanced or metastatic ER+, HER2– breast cancer that is not amenable to curative treatment. Participants must have progressed following



The study included the dose selection part where approximately 120 patients were randomized between 90 mg QD palazestrant, 120 mg QD palazestrant, or SOC ET. The dose of palazestrant 90 mg was selected based on safety, efficacy, pharmacokinetics, and patient-reported outcomes. Out of 510 patients to be enrolled in total, 470 patients will be randomized between 90 mg QD palazestrant or SOC ET.

†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.

Figure 2. OPERA-01 study design.

Abbreviations: ABC, advanced breast cancer; CDK4/6, cyclin-dependent kinase 4/6; CDK4/6i; cyclin-dependent kinase 4/6 inhibitor; ctDNA, circulating tumor DNA; ER+, estrogen receptor-positive; ESR1-mut, estrogen receptor 1 mutation; ESR1-mut-nd, estrogen receptor 1 mutation not detected; ET, endocrine therapy; GnRH, gonadotropin-releasing hormone; HER2–, human epidermal growth factor receptor 2-negative; IM, intramuscular; pt, patient; QD, once a day; SOC, standard-of-care.

Table 1. Key eligibility criteria for OPERA-01.

Inclusion criteria

- Male or female, age ≥18 years
- Histologically or cytologically confirmed adenocarcinoma of the breast with evidence of locally advanced or metastatic breast cancer that is not amenable to treatment
- Laboratory-confirmed ER+, HER2− breast cancer (per ASCO-CAP guidelines)
  - ≥ER positive staining by IHC
  - 0 or 1+ by IHC for HER2 membrane protein
- Evaluable disease:
  - ≤1 measurable lesion per RECIST v1.1, or
  - Bone-only disease with ≤1 radiographically evaluable lesion
- Prior treatment with 1 or 2 lines ET, including in combination with a CDK4/6 inhibitor for advanced or metastatic breast cancer
- ECOG PS ≥1
- Males and pre- or perimenopausal females must be willing to take a luteinizing hormone before the first dose of study treatment until the end of the treatment period
- Males and females of childbearing age must be willing to use effective contraception during the study and for 90 days or longer, following the last dose of study treatment
- Adequate hematologic, renal, hepatic, and coagulation function

Exclusion criteria

- Symptomatic visceral disease, imminent organ failure, or any disease burden causing ineligibility for ET; contraindications to the selected SOC ET
- Prior chemotherapy (including ADC) in the advanced/metastatic setting
- Treatment within the following windows prior to the first dose of study treatment:
  - Fulvestrant, <28 days prior
  - ET, CDK4/6i, everolimus, tacrolimus, alpelisib, or PARP inhibitors, <14 days prior
  - Any investigational cancer therapy, <28 days or 5 half-lives (whichever is shorter) prior
- Prior treatment with elacestrant or any investigational ER-directed therapy
- CNS metastases, carcinomatous meningitis, leptomeningeal disease, or spinal cord compression that requires immediate CNS-directed treatment
- Impaired cardiac function or clinically significant cardiac disease
- Cerebral vascular disease, pulmonary embolism, DVT <6 months prior to the first dose of study drug, or increased risk of thrombosis
- Have an active infection or at a high risk of developing serious infection during study treatment (e.g., participants with immunodeficiencies, uncontrolled diabetes mellitus, uncontrolled heart disease, poor general health, and poor nutritional status).

Abbreviations: ADC, antibody–drug conjugate; ASCO-CAP, American Society of Oncology-College of American Pathologists; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CNS, central nervous system; DVT, deep vein thrombosis; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ER, estrogen receptor; ER+, estrogen receptor-positive; ET, endocrine therapy; HER2, human epidermal growth factor receptor; HER2−, human epidermal growth factor receptor 2-negative; IHC, immunohistochemistry; PARP, poly(ADP-ribose) polymerase; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; SOC, standard-of-care.

treatment with the combination of ET and a CDK4/6i; one additional line of ET is allowed. Additional eligibility criteria are listed in Table 1. Enrollment began in November 2023. Approximately 510 participants are expected to be enrolled, including 470 for the primary analysis.

2.2.2. Treatment arms

Part 1 was a three-arm dose selection part, in which participants received palazestrant 90 mg QD, palazestrant 120 mg QD, or an investigator's choice of SOC ET (fulvestrant or anastrozole, letrozole, or exemestane).

The Independent Data Monitoring Committee recommended a 90-mg palazestrant QD dose based on the available safety, efficacy, patient-reported outcomes, and pharmacokinetic data from participants treated with palazestrant 90 mg and 120 mg in Part 1. In Part 2, participants receive once-daily palazestrant (90 mg QD) or SOC ET as described in Part 1. Fulvestrant or the AIs letrozole, anastrozole, or exemestane (with gonadal suppression in pre- and perimenopausal women or men) are included as the physician's choice of SOC ET monotherapy for the control arm. The SOC ET in the control arm aligns with the NCCN and ASCO guidelines recommending ET monotherapy as a treatment option to delay chemotherapy, supported by evidence demonstrating sustained endocrine sensitivity and responsiveness of ER+, HER2− breast cancer to fulvestrant, tamoxifen, or non-steroidal AIs ET, even after prior ET failures [16–18,45–51]. As a global study, the SOC control arm has been planned to account for regional variations in standard practices. The inclusion of AI monotherapy ensures consistency with guideline-supported treatment options across diverse clinical settings [16–18,49].

2.2.3. Randomization

Participants (N = 510 overall and 470 in the primary analysis) are randomized to treatment arms using Interactive Response Technology, and randomization is stratified based on 1) the presence of *ESR1*-mut or absence of detectable *ESR1* mutations (*ESR1*-mut-nd), assessed centrally on circulating tumor DNA (ctDNA) collected during screening period in line with NCCN Guidelines [16]; 2) prior lines of ET for advanced disease (1 vs 2); and 3) presence of visceral disease (yes vs no).

2.2.4. Endpoints

The dual primary endpoint of the overall study is blinded independent committee review (BICR)-assessed PFS, defined as the time from randomization to the date of the first documented progression or death due to any cause, in participants with *ESR1*-mut and *ESR1*-mut-nd tumors, to be assessed separately. Key secondary endpoints of overall survival (OS), defined as the time from randomization to the date of death due to any cause regardless of whether the patient withdraws from randomized therapy or receives another subsequent anti-cancer therapy, will be assessed separately in participants with *ESR1*-mut and *ESR1*-mut-nd tumors. Additional detailed outcomes are available in Table 2.

Table 2. OPERA-01 endpoints.

Primary endpoint
- BICR-assessed PFS in patients with *ESR1*-mut and *ESR1*-mut-nd tumors

Secondary endpoints
- OS in patients with *ESR1*-mut and *ESR1*-mut-nd tumors
- BICR-assessed PFS in the ITT population
- OS in the ITT population
- Investigator-assessed PFS in patients with *ESR1*-mut and *ESR1*-mut-nd tumors and in the ITT population
- BICR-assessed ORR, DoR, CBR
- Investigator-assessed ORR, DoR, CBR
- Safety and tolerability (AEs, SAEs, dose modifications, clinical laboratory parameters, ECGs, performance status, and vital sign measurements)
- PK parameters (including C_{max}, C_{min}, T_{max}, AUC, $t_{½}$, and palazestrant trough concentration at steady state)
- PROs (assessed using EQ-5D-5 L and EORTC QLQ-C30)

Exploratory endpoints
- Time to subsequent anticancer therapy
- PRO endpoints (assessed using PRO-CTCAE)
- Alterations in ctDNA or markers of oncogenic pathways, cell proliferation, and cell cycle and associations with clinical response
- Safety, efficacy, and PRO outcomes at the non-selected dose

Abbreviations: AE, adverse event; AUC, area under the curve; BICR, blinded independent committee review; CBR, clinical benefit rate; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; ctDNA, circulating tumor DNA; DoR, duration of response; ECG, electrocardiogram; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5 L, EuroQol 5 Dimension 5 Level; ESR1-mut, ESR1 mutated; ESR1-mut-nd; ESR1 mutation not detected; ITT, intent-to-treat; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; PRO, patient-reported outcome; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; SAE, serious AE; $t_{1/2}$, effective half-life; T_{max}, time to maximum plasma concentration.

2.3. Study procedures

Adverse event (AE) severity is determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0.

Tumor response and disease progression are assessed locally and centrally using body imaging by computed tomography (preferred) or magnetic resonance imaging. Baseline tumor imaging is performed during screening, within 28 days of randomization, and radiographic assessments are conducted periodically. After disease progression, participants are followed to assess survival status.

Health-related quality-of-life patient-reported outcomes (HRQoL PROs) are assessed using the EQ-5D-5 L, EORTC QLQ-C30, and PRO-CTCAE instruments. Pharmacokinetic (PK) parameters are determined using plasma levels of palazestrant from blood samples collected at protocol-defined timepoints.

An independent data monitoring committee (IDMC), comprising medical and statistical representatives not involved in the trial, is monitoring the safety, efficacy, and conduct of the trial. The dose selected for Part 2 of this study was recommended by the IDMC.

2.4. Statistical analyses

In Part 1 of the study, the selected dose was based on analyses of safety, preliminary efficacy, PK/pharmacodynamic (PD) parameters, and other relevant clinical and laboratory data, and there was no formal statistical comparison.

Blinded independent committee review (BICR)-assessed PFS, locally assessed PFS, and overall survival (OS) will be analyzed separately in participants with *ESR1*-mut tumors and participants with *ESR1*-mut-nd tumors by Kaplan–Meier (KM) methods; median and 95% confidence intervals (CIs) will be reported. Significant differences between treatment groups will be analyzed using the stratified log-rank test, stratified by a number of prior lines of ET and presence or absence of visceral metastases. Cox regression models will be used to estimate hazard ratios and 95% CIs.

Other secondary endpoints – overall response rate (ORR), CBR, and duration of response (DoR) – will be analyzed using both BICR- and investigator-assessed response evaluations.

3. Conclusion

There is an unmet need for novel therapies to overcome and suppress the development of ET resistance in patients with ER +, HER2– ABC, including those who acquire *ESR1* mutations. Preclinical data suggest that palazestrant, a novel oral CERAN and SERD, exhibits potent suppression of ER activity in tumors with and without *ESR1*. Furthermore, in early-phase clinical studies, palazestrant showed a tolerable safety profile, favorable pharmacokinetics, and encouraging antitumor efficacy in heavily pretreated patients, regardless of *ESR1* mutation status, providing support for further investigation.

3.1. Additional ongoing studies in advanced breast cancer

Given the tolerability and promising efficacy of palazestrant monotherapy and the potential for palazestrant to serve as a backbone ET for combination regimens, early-phase studies are evaluating combinations of palazestrant with CDK4/6i or

targeted therapies [52,53]. Ongoing phase Ib/II studies evaluating the combination of palazestrant with palbociclib (OP-1250–002; NCT05266105) or with ribociclib, alpelisib, everolimus, or atirmociclib (OP-1250-003; NCT05508906) in patients with pretreated ER+, HER2– ABC, including prior CDK4/6i, has demonstrated the feasibility of combining palazestrant with CDK4/6i [54,55]. In an analysis of the palazestrant in combination with ribociclib arm, palazestrant was well tolerated in all doses when combined with the full dose of ribociclib, and safety was consistent with the safety profile for each drug. Neutropenia (55%) was the most common grade 3–4 event in patients treated with palazestrant and ribociclib, compared to 60% observed in patients treated with ribociclib and SOC ET [56,57]. Median PFS (mPFS) was 15.5 months in all patients and 12.2 months in patients with prior CDK4/6i. In patients with prior CDK4/6i therapy, mPFS was 9.2 months in patients with *ESR1*-wt disease and 13.8 months in patients with *ESR1*-mut disease [56]. These ongoing studies support further clinical development of palazestrant-based combinations for first-line treatment of ER+, HER2– locally advanced or metastatic breast cancer.

3.2. Concluding remarks on the OPERA-01 study

The OPERA-01 study is an ongoing phase III study being conducted to investigate palazestrant monotherapy versus SOC ET in patients with ER+, HER2– locally advanced or metastatic breast cancer whose disease has advanced on ET in combination with a CDK4/6i. Findings from this study will provide insights into the safety and efficacy of palazestrant compared to SOC ET in patients with pretreated ER+, HER2– ABC, regardless of *ESR1* mutation status, potentially leading to a new and effective treatment option for this patient population.

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Ethical declaration

This trial is conducted in accordance with the Declaration of Helsinki and Good Clinical Practices (GCP) according to International Council on Harmonization (ICH) guidelines and applicable national regulations. The protocol was reviewed and approved by Internal Review Boards or Ethics Committees at each site prior to study activation. Participants are referred to the study investigator (if different from the medical provider), and written informed consent is provided by each participant prior to study entry. All records identifying participants are kept confidential and managed under the applicable laws and regulations. Study results will be shared in peer-reviewed articles, press releases, and at scientific congresses or meetings.

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