A Phase 1b/2 Study of Palazestrant (OP-1250) in Combination With Ribociclib in Patients With Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative (ER+/HER2−), Advanced and/or Metastatic Breast Cancer

Abstract P2-09-16

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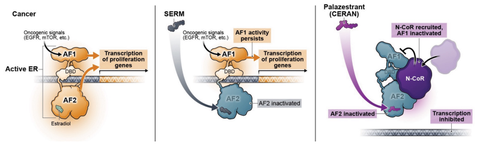
INTRODUCTION

- Palazestrant is a complete estrogen receptor (ER) antagonist (CERAN) and selective ER degrader (SERD); it blocks both transcriptional activation function domains, AF1 and AF2, of the ER.[1] (**Figure 1**)
- Palazestrant has demonstrated activity in both estrogen receptor 1 (*ESR1*)-wild type (*ESR1*-wt) and *ESR1*-mutant (*ESR1*-mut) preclinical models.[1]
- Palazestrant in combination with ribociclib resulted in enhanced tumor shrinkage and prolonged survival in both *ESR1*-wt and *ESR1*-mut xenograft models.[2,3]

Figure 1: Mechanism of action of palazestrant at the estrogen receptor[4]



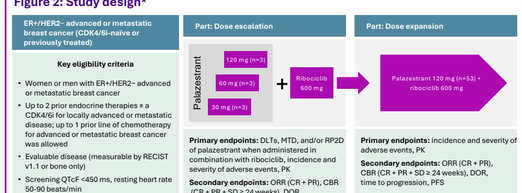
AF, activation function; **DBD**, DNA binding domain, **EGFR**, epidermal growth factor receptor, **ER**, estrogen receptor; **mTOR**, mammalian target of rapamycin; **N-CoR**, nuclear receptor corepressor; **SERM**, selective estrogen receptor modulator.

- Combination of an aromatase inhibitor (AI) with the cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) ribociclib is a standard-of-care (SOC) first-line treatment for ER+/HER2− advanced or metastatic breast cancer (mBC).[5]
- Endocrine resistance is a major challenge in treating ER+/HER2− mBC. Mutation in the *ESR1* gene is a key resistance mechanism.[6] Therapies that can overcome endocrine resistance are needed.
- The combination of palazestrant with ribociclib may have an advantage over SOC as initial treatment of ER+/HER2− mBC by completely inhibiting ER and suppressing the emergence of *ESR1* mutations.
- In a phase 1/2 study, palazestrant as monotherapy showed favorable safety, good tolerability, encouraging antitumor activity, and a pharmacokinetics profile supportive of once-daily (QD) oral dosing in patients with ER+/HER2− mBC.[7] A phase 3 study, OPERA-01, comparing palazestrant to SOC, is ongoing (NCT06016738).
- The recommended phase 2 dose (RP2D) of palazestrant as monotherapy or in combination with ribociclib is 120 mg QD.

METHODS

- Here, we present an update from the OP-1250-003 study of palazestrant in combination with ribociclib in patients with ER+/HER2− advanced or metastatic breast cancer.
- The OP-1250-003 study comprises a dose-escalation phase, followed by a dose expansion-phase. The study investigates palazestrant in combination with ribociclib, alpelisib, or everolimus. This analysis focuses on the palazestrant and ribociclib combination. (**Figure 2**)

Figure 2: Study design*



*For detailed information, refer to NCT05508906 on ClinicalTrials.gov (https://clinicaltrials.gov/study/NCT05508906).
CBR, clinical benefit rate; **CR**, complete response; **DLT**, dose-limiting toxicity; **DOR**, duration of response; **MTD**, maximum tolerated dose; **ORR**, objective response rate; **PFS**, progression-free survival; **PK**, pharmacokinetic; **PR**, partial response; **QTcF**, corrected QT interval; **RECIST v1.1**, Response Evaluation Criteria in Solid Tumors version 1.1. **SD**, stable disease.

DEMOGRAPHICS

- 62 patients were enrolled as of September 25, 2024. (**Table 1**)
- 3 patients received 30 mg QD palazestrant, 3 patients received 60 mg QD palazestrant, and 56 patients were treated at RP2D of 120 mg QD, all with the full dose of ribociclib.
- 46 (74%) patients received prior CDK4/6i with endocrine therapy for advanced disease. (**Table 1**)
  - 34 (55%) received 1 prior CDK4/6i (palbociclib, n=23; abemaciclib, n=7; ribociclib, n=4).
  - 12 (19%) received 2 prior CDK4/6i (palbociclib→palbociclib, n=3; palbociclib→abemaciclib, n=3; palbociclib→ribociclib, n=3; ribociclib→ribociclib, n=1; abemaciclib→palbociclib, n=1; palbociclib→an experimental CDK4/6i, n=1).

Table 1: Baseline demographics and disease characteristics

Characteristics	Total (N=62)
Median age, years (range)	61 (28-85)
Female sex, n (%)	62 (100%)
Premenopausal, n (%)	9 (15%)
ECOG performance status, n (%)	
0	38 (61%)
1	24 (39%)
Measurable disease at baseline, n (%)	42 (68%)
Visceral disease, n (%)	36 (58%)
Prior lines of therapy in advanced setting, n (%)	
0	14 (23%)
1	29 (47%)
2	14 (23%)
3	5 (8%)
Prior lines of endocrine therapy in advanced setting, n (%)	
0	14 (23%)
1	35 (56%)
2	13 (21%)
Types of prior therapy in advanced setting, n (%)	
CDK4/6 inhibitor	46 (74%)
Aromatase inhibitor	33 (53%)
Fulvestrant	25 (40%)
Chemotherapy	11 (18%)
ESR1* mutation at baseline	17/60 evaluated (28%)

Data cutoff: September 25, 2024.
**ESR1* mutations in ctDNA at baseline were determined centrally using SafeSEQ Breast Cancer Panel (Sysmex Inostics, Baltimore, MD). Two samples were not evaluable.
ctDNA, circulating tumor DNA; **ECOG**, Eastern Cooperative Oncology Group.

SAFETY AND TOLERABILITY

- 30 (48%) patients were still on treatment as of September 25, 2024.
- The longest duration of treatment is 72 weeks and ongoing.
- The most common reason for treatment discontinuation was disease progression.
- No dose-limiting toxicities were observed during the dose-escalation phase, and the maximum tolerated dose was not reached.
- The majority of treatment-emergent adverse events (TEAEs) were grade 1 and grade 2. (**Table 2**)
- No patients had a dose discontinuation or reduction of palazestrant only.
- 4 patients discontinued both treatments due to a TEAE, and 2 patients discontinued ribociclib only.
- 7 patients had a dose reduction of both treatments; 18 patients had a dose reduction of ribociclib. The most common cause for dose reduction was neutropenia.

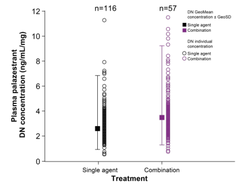
Table 2: TEAEs reported in ≥25% of patients

	Olema study 003 ribociclib + palazestrant (N=62)			MONALEESA-2 ribociclib + letrozole* (N=334)		
	All grades†	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Neutropenia‡	51 (82%)	28 (45%)	6 (10%)	93%§	49%	11%
Nausea	49 (79%)	2 (3%)	0%	52%	2%	0%
Fatigue	37 (60%)	2 (3%)	0%	37%	2%	<1%
Diarrhea	31 (50%)	2 (3%)	0%	35%	1%	0%
Anemia	27 (44%)	1 (2%)	0%	57%§	2%	0%
WBC decrease	26 (42%)	10 (16%)	1 (2%)	93%§	31%	3%
Constipation	24 (39%)	0%	0%	25%	1%	0%
Creatinine increased	20 (32%)	0%	0%	20%	0.6%	0%
Vomiting	20 (32%)	1 (2%)	0%	29%	4%	0%
Electrocardiogram QT prolonged	19 (31%)	3 (5%)	0%	43%‖	8%‖	NR
Arthralgia	18 (29%)	0%	0%	27%	0.9%	NR
Lymphocyte decreased	16 (26%)	4 (7%)	1 (2%)	51%§	12%	2%
Cough	16 (26%)	0%	0%	20%	0%	0%

Data cutoff: September 25, 2024.
Data shown are n or n (%). *Adverse reactions reported in ≥10% of patients who received ribociclib plus letrozole in the MONALEESA-2 study.[8,9] †Two patients experienced grade 5 AEs, heart failure not related to palazestrant and depressed level of consciousness not related to study drugs but disease progression. ‡Combined term includes neutropenia, decreased neutrophil count, and febrile neutropenia. §These values were taken from MONALEESA-2 lab abnormalities data.[8] ‖Ribociclib + fulvestrant in MONALEESA-3 per the Ribociclib Approval Package (NUMBER:209092Orig1s001, June 2018); ribociclib + nonsteroidal aromatase inhibitors in MONALEESA-7: all grade QTcF prolongation was 46.5% (grade 2, 5.3%; grade 3, 9%). Aggregate analysis (n=1054 patients).
AE, adverse event; **NR,** not reported; **QTcF,** corrected QT interval; **WBC,** white blood cell.

PHARMACOKINETICS

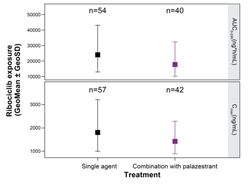
Figure 3: Pharmacokinetics of palazestrant as a single agent and in combination with ribociclib



- Steady-state trough values between the combination and single-agent palazestrant were overlapping.

Combination data cutoff: September 25, 2024. Single-agent data cutoff: February 28, 2024.
Pre-dose samples at C2D1, C2D15, C3D1, C5D1, C7D1, and C9D1 included for both studies.
DN, dose normalized; **GeoMean,** geometric mean; **GeoSD,** geometric standard deviation; **n,** number of observations.

Figure 4: Pharmacokinetics of ribociclib 600 mg as a single agent and in combination with palazestrant



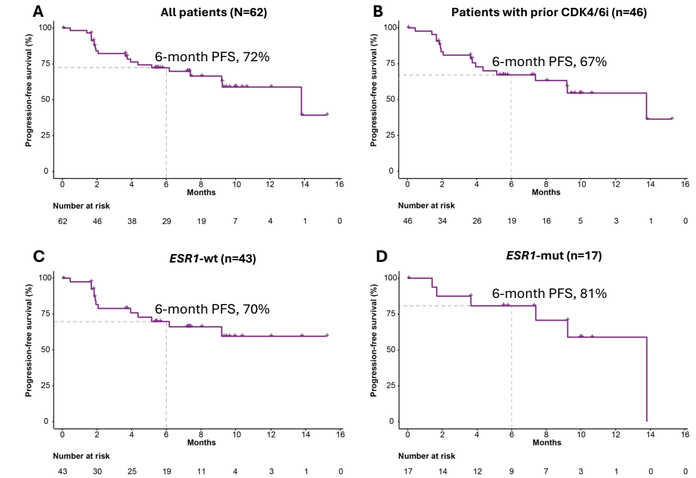
- Palazestrant did not affect ribociclib 600 mg exposure when compared with published concentrations for single-agent ribociclib.

Single-agent steady-state exposure levels for ribociclib from CLEE011X2101; Data cutoff: September 18, 2015.
AUC$_{0-24,ss}$ area under the curve from 0 to 24 hours; **C$_{max,ss}$**, maximum serum concentration; **GeoMean,** geometric mean; **GeoSD,** geometric standard deviation; **n,** number of observations.

EFFICACY

- With a median follow-up of 10 months, median PFS was not reached. (**Figure 5**)

Figure 5: PFS in all patients (A), patients with prior CDK4/6i (B), and patients with *ESR1*-wt disease (C) or *ESR1*-mut disease (D)

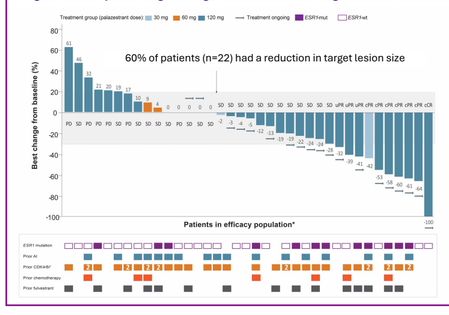


Data cutoff: September 25, 2024.
Follow-up was calculated from first dose date to data cutoff date regardless of disease progression status.
CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ***ESR1*,** estrogen receptor 1; ***ESR1*-mut,** *ESR1*-mutant; ***ESR1*-wt,** *ESR1*-wild type; **PFS,** progression-free survival.

- Clinical benefit rate (CBR)* was 76% in all patients, 81% with *ESR1*-mut and 74% with *ESR1*-wt mBC.
- Among patients with prior CDK4/6i, CBR* was 71% in all patients, 81% with *ESR1*-mut and 65% with *ESR1*-wt mBC.

*CBR is the proportion of patients who remained on treatment through at least 24 weeks with a confirmed complete response or partial response, or stable disease.

Figure 6: Best percentage change from baseline in target lesions and best overall response*



- 27% (10/37) objective response rate (ORR) among response-evaluable patients with measurable disease.
- 2 confirmed complete responses (cCRs); 6 confirmed partial responses (cPRs); 3 unconfirmed PRs (uPRs). (**Figure 6**)
- 30/62 patients (48%) remain on treatment; efficacy maturing.

Data cutoff: September 25, 2024.
*Waterfall plot n=37. †Patients who received 2 prior CDK4/6is in the metastatic setting are indicated with a 2.
PD, progressive disease; **SD,** stable disease.

CONCLUSIONS

- Palazestrant was well tolerated in all doses when combined with the full dose of ribociclib.
- Safety was consistent with the known safety profiles of each drug.
- Encouraging preliminary efficacy from the combined agents, including in patients with prior CDK4/6i treatment, was observed.
  - Median PFS was not reached.
  - 6-month PFS rate was 72% in all patients, 67% with prior CDK4/6i, 70% with *ESR1*-wt and 81% with *ESR1*-mut mBC.
  - CBR was 76% in all patients, 71% with prior CDK4/6i, 74% with *ESR1*-wt and 81% with *ESR1*-mut mBC.
- This study supports further clinical development of palazestrant in combination with ribociclib for the first-line treatment of ER+/HER2− advanced or metastatic breast cancer.

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