

Palazestrant (OP-1250) plus ribociclib in patients with estrogen receptor-positive, human epidermal growth factor receptor 2-negative (ER+, HER2–) advanced breast cancer (ABC)

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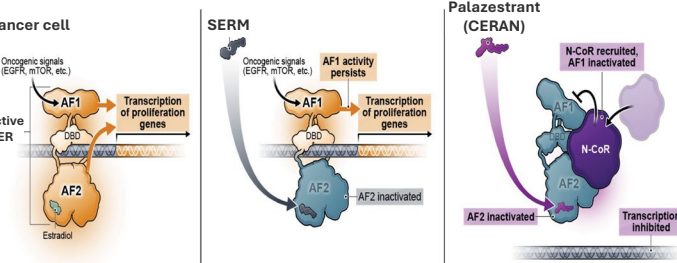
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INTRODUCTION

- Palazestrant is a complete estrogen receptor antagonist (CERAN) and selective estrogen receptor degrader (SERD); it blocks both transcriptional activation function domains, AF1 and AF2, of the ER.^{1,2} (**Figure 1**)
- Palazestrant has 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.³

Figure 1: Mechanism of action of palazestrant at the estrogen receptor⁴

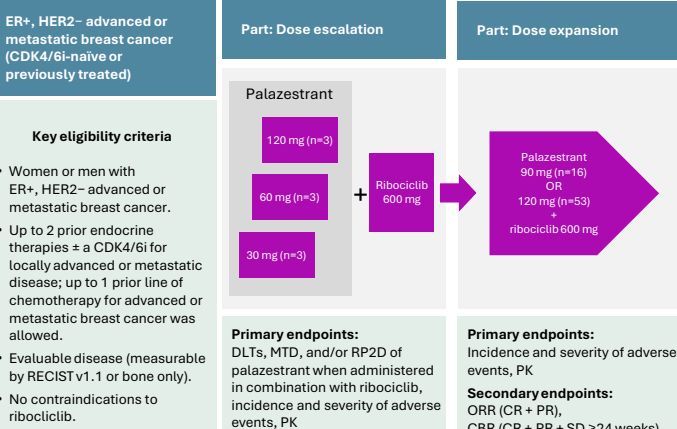


- Endocrine resistance is a major challenge in treating ER+, HER2– ABC. Mutation in the *ESR1* gene is a key resistance mechanism.⁵ Therapies that can overcome endocrine resistance are needed.
- The combination of palazestrant with ribociclib may have an advantage over SOC as initial treatment of ER+, HER2– ABC 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– ABC.⁴ A phase 3 study, OPERA-01, comparing palazestrant to SOC, is ongoing (NCT06016738).
- Palazestrant monotherapy resulted in a median progression-free survival (PFS) of 4.8 months (95% CI, 3.5–7.1) for all patients, and 5.6 months (95% CI, 4.8–NE) among patients with *ESR1*-mut disease. Most treatment-emergent adverse events (TEAEs) were grade 1 and 2.⁴
- Here, we present an update from the OP-1250-003 study of palazestrant in combination with ribociclib in patients with ER+, HER2– ABC.

METHODS

- 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 <https://clinicaltrials.gov/study/NCT06058906>. CBR, clinical benefit rate; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CR, complete response; DLT, dose-limiting toxicity; DOR, duration of response; ER+, estrogen receptor-positive; HER2–, human epidermal growth factor receptor-negative; MTD, maximum tolerated dose; ORR, objective response rate; PFS, progression-free survival; PK, pharmacokinetic; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RP2D, recommended phase 2 dose; SD, stable disease.

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DEMOGRAPHICS

- 78 patients were enrolled in the dose-expansion and dose-escalation cohorts as of July 8, 2025.
- Here we present the data for 72 patients: 56 patients received 120 mg QD palazestrant and 16 patients received 90 mg QD palazestrant, all with 600 mg of ribociclib.
- 39 (54%) patients had visceral disease, 49 (68%) had measurable disease, and 48 (67%) received prior endocrine therapy for advanced disease. (**Table 1**)
- 45 (63%) patients (40 patients at 120 mg; 5 patients at 90 mg) received prior CDK4/6i with endocrine therapy for advanced disease.
 - 36 (50%) received 1 prior CDK4/6i (palbociclib, n=23; abemaciclib, n=8; ribociclib, n=5).
 - In the 120 mg cohort, 9 (13%) received 2 prior CDK4/6i (palbociclib→palbociclib, n=2; palbociclib→abemaciclib, n=2; palbociclib→ribociclib, n=3; ribociclib→ribociclib, n=1; abemaciclib→palbociclib, n=1).
- At baseline, 22% (15/69) of all patients had tumors with *ESR1* mutations; 33% (15/45) of patients with one prior line of therapy in the advanced setting (2L/3L+) had tumors with *ESR1* mutations.

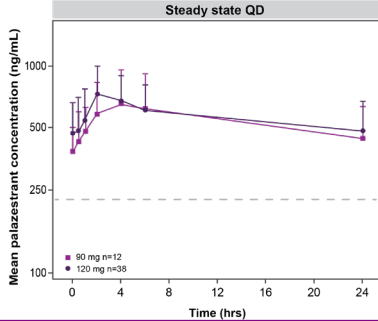
Table 1: Baseline demographics and disease characteristics

Characteristics	Palazestrant dose		
	90 mg (n=16)	120 mg (n=56)	Total (N=72)
Median age, yrs (range)	60 (25-76)	61 (28-85)	61 (25-85)
Female sex, n (%)	16 (100%)	56 (100%)	72 (100%)
Premenopausal, n (%)	4 (25%)	8 (14%)	12 (17%)
ECOG Performance Status, n (%)			
0	10 (63%)	34 (61%)	44 (61%)
1	6 (38%)	22 (39%)	28 (39%)
Measurable disease at baseline, n (%)	12 (75%)	37 (66%)	49 (68%)
Visceral disease, n (%)	6 (38%)	33 (59%)	39 (54%)
Prior lines of therapy in advanced setting, n (%)			
0	10 (63%)	14 (25%)	24 (33%)
1	5 (31%)	26 (46%)	31 (43%)
2	1 (6.3%)	12 (21%)	13 (18%)
3	0	4 (7%)	4 (6%)
Prior lines of endocrine therapy in advanced setting, n (%)			
0	10 (63%)	14 (25%)	24 (33%)
1	6 (38%)	32 (57%)	38 (53%)
2	0	10 (18%)	10 (14%)
Types of prior therapy in advanced setting, n (%)			
CDK4/6 inhibitor	5 (31%)	40 (71%)	45 (63%)
Aromatase inhibitor	5 (31%)	27 (48%)	32 (44%)
Fulvestrant	1 (6%)	22 (39%)	23 (32%)
Chemotherapy	1 (6.3%)	10 (18%)	11 (15%)
<i>ESR1</i> mutation at baseline*	1/15 (7%)	14/54 (26%)	15/69 (22%)

Data cutoff: July 8, 2025. **ESR1* mutations in cDNA at baseline were determined centrally using SafeSeq Breast Cancer Panel (Syngene Inotivics, Baltimore, MD). Three samples were not evaluable. CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; cDNA, circulating tumor DNA; ECOG, Eastern Cooperative Oncology Group; *ESR1*, estrogen receptor 1.

PHARMACOKINETICS

Figure 4: Palazestrant doses of 90 mg and 120 mg had overlapping exposure when in combination with ribociclib



- Steady-state plasma concentrations at both 90 mg and 120 mg doses exceeded the predicted efficacious threshold
- Ribociclib had no clinically meaningful effect on palazestrant exposure

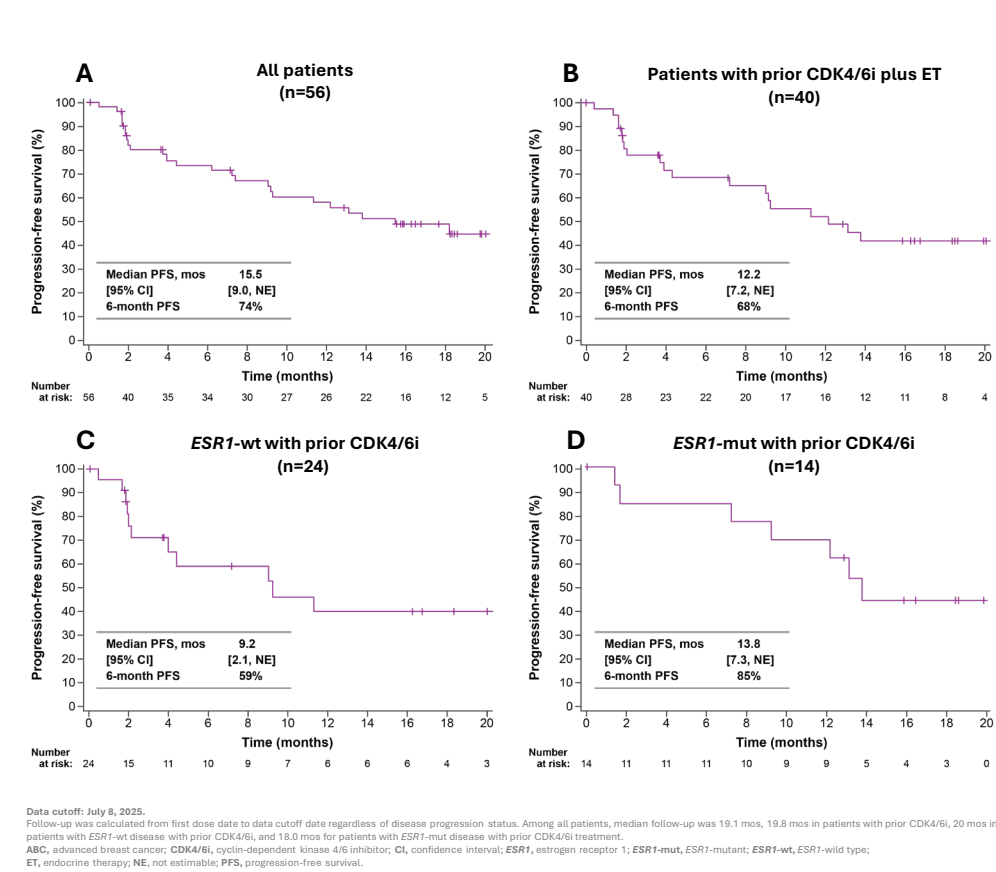
Data cutoff: July 18, 2025. Data are arithmetic mean and SD; the dashed line indicates the target (efficacious) exposure based on extradiol-supplemented preclinical models (C_{min}: 226 ng/mL).⁶ Rich pharmacokinetic samples collected at cycle 2 day 15. C_{min}, minimum plasma concentration; QD, once daily.

Acknowledgments

We thank the OP-1250-003 trial patients, their families and caregivers, trial investigators, and study staff. This study was sponsored by Olema Oncology. Medical writing and editorial support were provided by Leslie Mitchell, PhD, and Adam Santanasto, PhD, MPH, of Petauri and funded by Olema Oncology.

EFFICACY

Figure 3: Palazestrant in combination with ribociclib demonstrated activity across all patients, including in *ESR1*-wt and *ESR1*-mut subpopulations post CDK4/6i



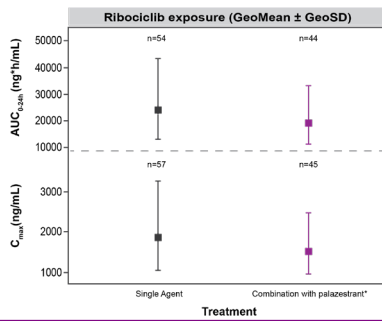
- For patients in the palazestrant 120 mg dose cohort, median PFS was 15.5 mos for all patients, 12.2 mos with prior CDK4/6i, 9.2 mos for *ESR1*-wt with prior CDK4/6i, and 13.8 mos for *ESR1*-mut with prior CDK4/6i-treated ABC. (**Figure 3**)
- In the 90 mg palazestrant dose cohort, the median follow-up was 10.8 months. The median PFS was not reached.
- 34% (15/44) objective response rate (ORR) among response-evaluable patients with measurable disease. (**Table 2**)
- 26% (6/23) ORR among patients with prior CDK4/6i, including 6 confirmed partial responses (cPRs) in the 120 mg cohort.
- The longest duration of treatment in the 120 mg cohort is 103 weeks and ongoing.
- 42% (30/72) patients remain on treatment; efficacy maturing.

Table 2: Overall response rate

	90 mg cohort (n=12)	120 mg cohort (n=32)	Prior CDK4/6i 120 mg cohort (n=23)	All (n=44)
cCR	1	1	0	2
cPR	4	9	6	13
ORR (n/n)	42% (5/12)	31% (10/32)	26% (6/23)	34% (15/44)

Data cutoff: July 8, 2025. cCR, confirmed complete response; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; cPR, confirmed partial response; ORR, overall response rate.

Figure 5: No significant drug-drug interaction was observed between palazestrant and ribociclib



- Palazestrant had no clinically meaningful effect on ribociclib 600 mg steady-state exposure when compared with published concentrations for single-agent ribociclib.

Data cutoff: July 18, 2025. Single-agent steady-state exposure levels for ribociclib from CLEO11X2101; Data cutoff: September 18, 2015. Ribociclib 600 mg QD was administered for 21 consecutive days followed by 7 days off treatment. AUC_{0-24h}, area under the curve from 0 to 24 hours; C_{min}, minimum serum concentration; GeoMean, geometric mean; GeoSD, geometric standard deviation, n=number of patients.

Disclosures

Dr. Lin reports consulting honoraria from Puma, Seattle Genetics, Daiichi-Sankyo, AstraZeneca, Denali Therapeutics, Prelude Therapeutics, Olema Oncology, Aleta BioPharma, Affinia Therapeutics, Voyager Therapeutics, Janssen, Blueprint Medicines, Stemline/Menarini, Artera Inc., and Reverie Labs. She has received institutional research support from Genentech, Pfizer, Merck, Seattle Genetics, Zion Pharmaceuticals, Olema Oncology, and AstraZeneca.

Poster presented at: European Society for Medical Oncology Congress; October 17-21, 2025; Berlin, Germany.

SAFETY AND TOLERABILITY

- 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 related TEAEs were grade 1 and 2. (**Table 3**)
- 2 patients had a dose reduction of palazestrant only; 1 due to nausea and 1 due to neutropenia (ribociclib treatment was held and never restarted in the patient experiencing neutropenia).
- 8 patients had a dose reduction of both treatments; 23 patients had a dose reduction of ribociclib. The most common cause for dose reduction was neutropenia.

Table 3: Related treatment-emergent adverse events reported in ≥25% of patients

Related TEAEs reported in ≥25% of patients	Palazestrant + ribociclib 120 mg (n=56)			Palazestrant + ribociclib 90 mg (n=16)			MONALEESA-2* Letrozole + ribociclib [†] (N=334)		
	All grades [‡]	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Neutropenia [§]	47 (84%)	28 (50%)	5 (9%)	13 (81%)	9 (56%)	2 (16%)	93% [‡]	49%	11%
Nausea	41 (73%)	2 (4%)	0	11 (69%)	1 (6%)	0	52%	2%	0%
Fatigue	30 (54%)	3 (5%)	0	9 (50%)	0	0	37%	2%	<1%
WBC decrease	24 (43%)	9 (16%)	1 (2%)	6 (38%)	4 (25%)	0	93% [‡]	31%	3%
Diarrhea	24 (43%)	2 (4%)	0	4 (25%)	0	0	35%	1%	0%
Anemia	22 (39%)	2 (4%)	0	5 (31%)	0	0	57% [‡]	2%	0%
Vomiting	21 (38%)	1 (2%)	0	4 (25%)	0	0	29%	4%	0%
Electrocardiogram QT prolonged	16 (29%)	4 (5%)	0	4 (25%)	1 (6%)	0	43% [‡]	8% [‡]	NR
Lymphocyte decrease	16 (29%)	3 (5%)	1 (2%)	3 (19%)	0	0	51% [‡]	12%	2%
AST increased	15 (27%)	2 (4%)	0	3 (19%)	0	0	44% [‡]	6%	1%
Constipation	15 (27%)	0	0	3 (19%)	0	0	25%	1%	0%

Data cutoff: July 8, 2025. Data shown are n or n (%). *This analysis is the aggregation of results across independent studies. There are risks inherent in conducting cross-trial comparisons and results should be interpreted with caution. [†]Adverse reactions reported in ≥10% of patients who received ribociclib plus letrozole in the MONALEESA-2 study.^{1,†} Three patients discontinued both treatments due to a TEAE (depression Gr 3, n=1; neutropenia Gr 4, n=1; vomiting and febrile neutropenia both Gr 3, n=1) and 2 patients discontinued ribociclib only (neutropenia Gr 4, n=2; fatigue Gr 3, n=1). Two patients experienced Gr 5 AEs: organ failure, and depressed level of consciousness; none of which were related to palazestrant. [‡]Combined term includes neutropenia, decreased neutrophil count, and febrile neutropenia. [§]These values were taken from MONALEESA-2 lab abnormalities data and the Ribociclib Approval Package (NUMBER:20902201g14001; June 2018). Ribociclib + fulvestrant in MONALEESA-3 per the Ribociclib Approval Package (NUMBER:20902201g14001; June 2018); ribociclib + nonsteroidal aromatase inhibitors in MONALEESA-7; all grade QTcF prolongation was 46.5% (Gr 2, 5.3%; Gr 3, 9%). Aggregate analysis (n=1054 patients). AE, adverse event; AST, aspartate aminotransferase; Gr, grade; NR, not reported; QTcF, corrected QT interval; TEAE, treatment-emergent adverse event; WBC, white blood cell.

CONCLUSIONS

- Palazestrant was well tolerated when combined with 600 mg of ribociclib.
- Safety was consistent with the known safety profiles of each drug; palazestrant and ribociclib did not demonstrate any drug-drug interactions.

- Encouraging preliminary efficacy from the combination at both the 90 mg and 120 mg dose of palazestrant, including in patients with prior CDK4/6i treatment, was observed.

– In the 90 mg palazestrant dose cohort, 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.

- The phase 3 dose of palazestrant as monotherapy or in combination with ribociclib is 90 mg QD. There was no clinically significant difference in exposure between 90 mg and 120 mg doses.
- This study supports the ongoing phase 3 OPERA-02 (NCT07085767) study evaluating 90 mg QD palazestrant in combination with ribociclib for the first-line treatment of ER+, HER2– advanced breast cancer.

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