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, Advanced and/or Metastatic Breast Cancer

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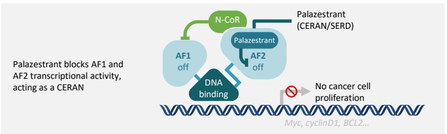
Introduction

- Addition of cyclin-dependent kinase 4/6 (CDK4/6) inhibitors to endocrine therapy has improved outcomes in patients with hormone receptor-positive (HR+) advanced or metastatic breast cancer, and is the current standard of care for first-line treatment.[1]
- Resistance to this first-line treatment eventually develops, with mutations in the estrogen receptor 1 *(ESR1)* gene constituting the most common mechanism.[2] The ability to suppress the activity of both wild-type and *ESR1*-mutant estrogen receptors (ER) represents the potential to significantly improve current first-line standard of care.
- Palazestrant is a complete ER antagonist (CERAN) and selective ER degrader (SERD); it blocks AF1 and AF2 transcriptional activation domains of the ER.[3] (**Figure 1**)
- Palazestrant has demonstrated activity in both *ESR1* wild-type and *ESR1* mutant preclinical models.[3]

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



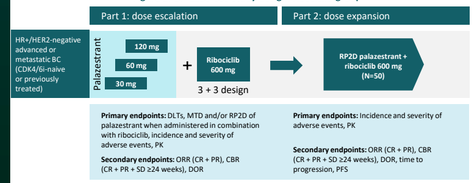
AF, activation function; **CERAN**, complete estrogen receptor antagonist; **N-CoR**, nuclear receptor corepressor; **SERD**, selective estrogen receptor degrader.

- Palazestrant in combination with ribociclib resulted in enhanced tumor shrinkage and prolonged survival in both ERα wild-type and mutant xenograft models.[5,6]
- In a phase 1/2 study, palazestrant as monotherapy (NCT04505826) demonstrated favorable safety, good tolerability, and a pharmacokinetics profile supportive of once-daily oral dosing in patients with ER+/human epidermal growth factor receptor 2-negative (HER2–) advanced or metastatic breast cancer. Median progression-free survival of 4.6 months and clinical benefit rate of 40% were observed in these heavily pretreated patients.[7]
- The recommended phase 2 dose (RP2D) of palazestrant for monotherapy was established as 120 mg once daily (QD), and the RP2D for palazestrant in combination with palbociclib was also determined to be 120 mg QD.
- Here we present an initial analysis of palazestrant in combination with ribociclib. Dose escalation is ongoing in the alpelisib treatment group and will be reported separately.

Methods

- The OP-1250-003 study comprises a dose-escalation phase followed by a dose-expansion phase. The study investigates two treatment groups: palazestrant in combination with ribociclib, and palazestrant in combination with alpelisib. This analysis focuses on the palazestrant and ribociclib combination. (**Figure 2**)

Figure 2. OP-1250-003 study design: ribociclib group



BC, breast cancer; **CBR**, clinical benefit rate; **CDK4/6i**, cyclin-dependent kinase 4/6 inhibitor; **CR**, complete response; **DLT**, dose-limiting toxicity; **DOR**, duration of response; **HER2**, human epidermal growth factor receptor 2; **HR+**, hormone receptor-positive; **MTD**, maximum tolerated dose; **ORR**, objective response rate; **PFS**, progression-free survival; **PK**, pharmacokinetics; **PR**, partial response; **RP2D**, recommended phase 2 dose; **SD**, stable disease.

Patient Population

Key eligibility criteria

- Women (regardless of menopausal status) or men with ER+/HER2– advanced or metastatic breast cancer
- Zero to two prior endocrine therapies ± a CDK4/6 inhibitor for locally advanced or metastatic disease. One prior line of chemotherapy for advanced or metastatic breast cancer was allowed
- Evaluable disease (measurable by RECIST 1.1 or bone only)
- Screening QTcF <450 ms, resting heart rate 50-90 beats/min

Results

- 10 patients were on treatment for 4 weeks or longer as of September 29, 2023. (**Table 1**)
  - The dose-escalation part included three dose cohorts (three patients per cohort): palazestrant at 30, 60, and 120 mg once daily plus ribociclib 600 mg once daily on days 1–21 of each 28-day treatment cycle (**Figure 2**). The RP2D of palazestrant was 120 mg in combination with ribociclib.
  - In the dose-expansion part (ongoing), patients receive palazestrant 120 mg plus ribociclib 600 mg. Of the 10 patients who were on treatment for 4 weeks or longer, one has been enrolled in the dose-expansion part.
- All patients received prior treatment with CDK4/6 inhibitors in combination with endocrine therapy for advanced disease.
  - All patients received prior palbociclib for advanced disease.
  - Three patients received prior lines of treatment for advanced disease that included two CDK4/6 inhibitors (palbociclib and abemaciclib, n=1; palbociclib and ribociclib, n=1; palbociclib and an experimental CDK4/6 inhibitor, n=1).

Table 1. Baseline patient demographics and disease characteristics

Characteristic	Total (N=10)
Median age, years (range)	57 (43–72)
Female sex	10 (100)
Premenopausal	1 (10)
ECOG performance status	
0	4 (40)
1	6 (60)
Measurable disease	8 (80)
Visceral disease	3 (30)
Prior lines of therapy for advanced disease	
0	0
1	5 (50)
2	3 (30)
3	2 (20)
Prior lines of endocrine therapy for advanced disease	
0	0
1	6 (60)
2	4 (40)
Types of prior therapy for advanced disease	
CDK4/6 inhibitor	10 (100)
Aromatase inhibitor	9 (90)
Fulvestrant	4 (40)
Chemotherapy	3 (30)
ESR1 mutations (ctDNA) at baseline	4/10 (40)[a]

Data shown are n (%) or n/N (%) unless otherwise specified.
[a]*ESR1* mutations in ctDNA at baseline were determined centrally using SafeSEQ Breast Cancer Panel (Sysmex Inostics, Baltimore, MD).

CDK4/6, cyclin-dependent kinase 4/6; **ctDNA**, circulating tumor DNA; **ECOG**, Eastern Cooperative Oncology Group; ***ESR1***, estrogen receptor 1 gene.

Patient Disposition

Table 2. Patient disposition

Treatment status	Palazestrant dose 30 mg (n=3)	60 mg (n=3)	120 mg (n=4)	Total (n=10)
Treatment ongoing	1	2	4	7 (70)
Treatment discontinued	2	1	0	3 (30)
Reason for treatment discontinuation				
Disease progression	2	1	0	3 (30)

Data shown are n or n (%).

Safety and Tolerability

- No dose-limiting toxicities were observed during the dose-escalation phase (the DLT observation period was at least 4 weeks), and the maximum tolerated dose was not reached.
- The majority of treatment-emergent adverse events (TEAEs) were grade 1 or grade 2. (**Table 3**)
- No QTcF values of >500 ms were observed at any time point.
- **No grade 4 TEAEs were reported.**

Table 3. Treatment-emergent adverse events (TEAEs) reported in ≥20% of patients

TEAE	Palazestrant dose 30 mg (n=3) All grades	30 mg (n=3) Grade 3	60 mg (n=3) All grades	60 mg (n=3) Grade 3	120 mg (n=4) All grades	120 mg (n=4) Grade 3	Total (n=10) All grades	Total (n=10) Grade 3
Neutropenia[a]	3	3	2	0	2	1	7 (70)	4 (40)
Nausea	3	0	1	0	2	0	6 (60)	0
Constipation	2	0	1	0	1	0	4 (40)	0
Fatigue	1	0	1	0	2	0	4 (40)	0
Anemia	0	0	2	0	1	0	3 (30)	0
Diarrhea	1	0	1	0	1	0	3 (30)	0
Hyperglycemia	0	0	1	0	2	0	3 (30)	0
Hypotension	1	0	1	0	1	0	3 (30)	0
WBC count decreased	0	0	2	0	1	0	3 (30)	0
Abdominal pain	0	0	1	0	1	0	2 (20)	0
Dizziness	1	0	1	0	0	0	2 (20)	0
Hypertension	1	0	0	0	1	0	2 (20)	0
Weight decreased	1	0	0	0	1	0	2 (20)	0

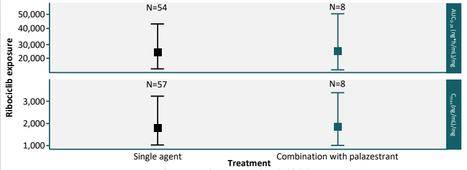
Data shown are n or n (%).
[a]Combined term includes both neutropenia and decreased neutrophil count.

- No patients discontinued due to an adverse event.
- There were no dose reductions of palazestrant or ribociclib within the 60 mg and 120 mg cohorts.
- In the 30 mg cohort, three patients had dose reductions due to grade 3 neutropenia: two patients had dose reductions of both palazestrant and ribociclib; one patient had a dose reduction of ribociclib only.
- Neutropenia was reversible in all patients and the timing was consistent with the ribociclib-related neutropenia.[8,9]

Pharmacokinetics

- Ribociclib 600 mg exposure is not affected by palazestrant doses ranging from 30 to 120 mg.
- Ribociclib is metabolized mainly by CYP3A4. Palazestrant is not a CYP3A4 inhibitor or inducer.
- When administered in combination with palazestrant, ribociclib exposure was within the reported range of the 600 mg dose single agent exposures at steady state. (**Figure 3**)

Figure 3. Steady-state exposure of ribociclib 600 mg



Data are geometric mean ± geometric standard deviation.
$AUC_{0\text{-}24}$, area under the curve from 0 to 24 h; C_{max}, maximum concentration.

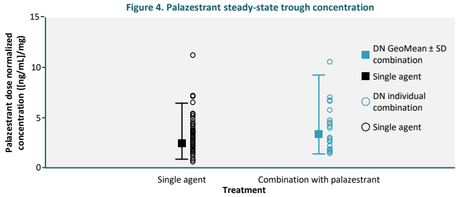
Table 4. Steady-state exposure of ribociclib 600 mg

Steady-state PK parameters	Ribociclib single agent[a]	Ribociclib in combination with palazestrant[b]
$AUC_{0\text{-}24}$ ([h*ng/mL]/mg), GeoMean (GeoCV); N	23,800 (66%); 54	25,400 (78%); 8
C_{max} (ng/mL/mg), GeoMean (GeoCV); N	1,820 (62%); 57	1,860 (66%); 8
T_{max} (h), Median (min–max); N	2.4 (0.68–7.8); 57	4.0 (1.0–6.0); 8

[a]Single agent steady-state exposure levels for ribociclib[10]
[b]Steady-state data from eight patients (two, 30 mg; three, 60 mg; three, 120 mg palazestrant); date of data cutoff: October 11, 2023.
$AUC_{0\text{-}24}$, area under the curve from 0 to 24 h; C_{max}, maximum concentration; **CSR**, clinical study report; **GeoCV**, geometric coefficient of variation; **GeoMean**, geometric mean; **max**, maximum; **min**, minimum; T_{max}, time to maximum concentration.

- Steady-state trough values overlapped between the combination and single agent palazestrant, with a small increase in mean exposure (**Table 4**). **The effect of ribociclib on the exposure of palazestrant is not clinically meaningful.**
- Ribociclib is a strong inhibitor of CYP3A4. While palazestrant is metabolized by CYP3A4, it is not sensitive to CYP3A4 inhibition.

Figure 4. Palazestrant steady-state trough concentration



Note: Predose samples at C2D1, C2D15, C3D1, and C5D1 for both studies.
Date of data cutoff: October 11, 2023.
DN, dose normalized; **GeoMean**, geometric mean; **SD**, geometric standard deviation.

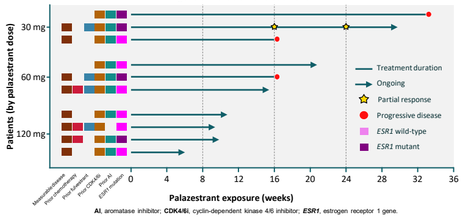
Table 5. Palazestrant steady-state trough concentration values

OP-1250-001 Single agent	OP-1250-003 Combination
2.49 (48%); 172 [2.35, 2.64]	3.35 (61%); 25 [2.77, 4.06]

Statistics: Geometric mean (geometric standard deviation); n [lower 90% confidence interval, upper 90% confidence interval].

Duration of Treatment

Figure 5. Duration of treatment



AI, aromatase inhibitor; **CDK4/6i**, cyclin-dependent kinase 4/6 inhibitor; ***ESR1***, estrogen receptor 1 gene.

- Data are maturing; 7/10 patients (70%) remain on treatment.
- The longest duration of treatment is 34 weeks.
- A confirmed partial response has been observed in one patient.

Conclusions

- The combination of palazestrant at 30–120 mg with ribociclib 600 mg was well tolerated; no new safety signals or enhancement of toxicity were identified.
  - The adverse event incidence and severity were consistent with the expected safety profile of ribociclib plus endocrine therapy, and were similar to those reported previously.[8]
- Palazestrant does not affect ribociclib exposure.
- Ribociclib has no clinically meaningful effect on palazestrant exposure.
- The overall safety profile, absence of maximum tolerated dose, and consistent drug exposure support the use of palazestrant at the RP2D of 120 mg in combination with ribociclib 600 mg.
- Enrollment in the dose-expansion part is ongoing at the RP2D of palazestrant in combination with ribociclib.
- Findings from this study support the further clinical development of palazestrant in combination with CDK4/6 inhibitors for the first-line treatment of ER+/HER2– advanced or metastatic breast cancer.

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