A Phase 1b/2 Study of Palazestrant (OP-1250), an Oral Complete Estrogen Receptor Antagonist (CERAN) and Selective ER Degrader (SERD), With Palbociclib in ER-Positive, HER2-Negative, Advanced or Metastatic Breast Cancer Patients

PS15-04

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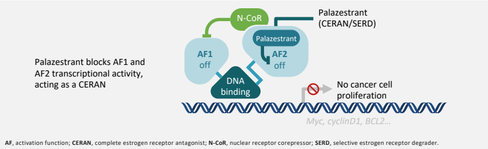
Introduction

- Endocrine therapy, when combined with cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, results in improved outcomes in patients with hormone receptor-positive (HR+) advanced or metastatic breast cancer; it is the current standard of care for first-line treatment.[1]
- Mutations of the estrogen receptor 1 *(ESR1)* gene often develop after this first-line regimen, constituting the most common mechanism of resistance for estrogen receptor (ER)-positive disease.[2] Suppressing activity of both wild-type and *ESR1*-mutant ER carries the potential to significantly improve upon current standard of care.
- Palazestrant is a complete ER antagonist (CERAN) and selective ER degrader (SERD), binds the ligand-binding domain of ER and completely blocks ER-driven transcriptional activity in both wild-type (*ESR1*-wt) and mutant (*ESR1*-mut) forms of ER.[3] (**Figure 1**)

Figure 1. Mechanism of action of palazestrant at the estrogen receptor[4,5]



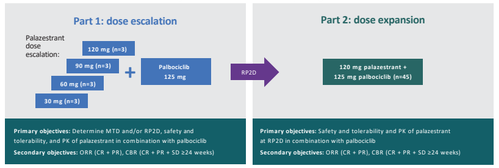
AF, activation function; **CERAN**, complete estrogen receptor antagonist; **N-CoR**, nuclear receptor corepressor; **SERD**, selective estrogen receptor degrader.

- In xenograft studies of both *ESR1* wild-type and mutant breast cancer models, the combination of palazestrant and palbociclib resulted in improved antitumor efficacy and a greater-than-additive suppression of transcription associated with cell cycle progression.[6]
- In a phase 2 monotherapy study, palazestrant demonstrated acceptable safety, good tolerability, and a pharmacokinetics (PK) 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 this heavily pretreated patient population.[7]
- Previous data from this open-label study of palazestrant in combination with the CDK4/6 inhibitor palbociclib in patients with ER+/HER2– metastatic breast cancer (NCT05266105) established favorable safety, PK, and antitumor activity, with no drug–drug interactions.[8]
- **Here, we present updates on safety, efficacy, and PK from the phase 1b/2 study of palazestrant in combination with palbociclib.**

Methods

The OP-1250-002 study comprises two parts: a dose-escalation phase followed by a dose-expansion phase. (**Figure 2**)

Figure 2. OP-1250-002 study design



CBR, clinical benefit rate; **CR**, complete response; **MTD**, maximum tolerated dose; **ORR**, objective response rate; **PK**, pharmacokinetic; **PR**, partial response; **RP2D**, recommended phase 2 dose; **SD**, stable disease.

Key eligibility criteria

- Women (regardless of menopausal status) or men with HR+/HER2– advanced or metastatic breast cancer
- Zero or one prior endocrine therapy ± 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 or non-measurable by RECIST 1.1)

Patient Population

- 46 patients were enrolled at 8 sites between January 2022 and August 2023. Data cutoff date for this analysis was September 15, 2023. (**Table 1**)
  - Dose-escalation included four dose cohorts (3 patients per cohort). Patients received 30, 60, 90, or 120 mg palazestrant QD plus 125 mg palbociclib PO QD on days 1–21 of each 28-day treatment cycle. (**Table 2**)
  - Dose-expansion (ongoing) patients receive 120 mg palazestrant plus 125 mg palbociclib QD. Thirty-four patients were enrolled in this part; approximately 45 patients are planned for enrollment in the dose-expansion phase.
- 40 (87%) patients received prior endocrine therapy for advanced disease.
- 33 (72%) patients received prior treatment with CDK4/6 inhibitors for advanced disease (palbociclib, n=22; ribociclib, n=10; both palbociclib and ribociclib, n=1).

Table 1. Baseline patient demographics and disease characteristics

Characteristic	Total (N=46)
Median age, years (range)	63.5 (30–77)
Female sex	45 (98)
Premenopausal	4 (9)
ECOG performance status	
0	31 (67)
1	15 (33)
Measurable disease	36 (78)
Visceral disease	20 (44)
Prior lines of therapy for advanced disease	
0	4 (9)
1	34 (74)
2	8 (17)[a]
Prior lines of endocrine therapy for advanced disease	
0	6 (13)
1	40 (87)
Types of prior therapy for advanced disease	
CDK4/6 inhibitor	33 (72)
Aromatase inhibitor	35 (76)
Fulvestrant	5 (11)
Chemotherapy	10 (22)
ESR1 mutation at baseline (ctDNA)	16/37 (43)[b]

Data shown are n (%) or n/N (%) unless otherwise specified.
[a]One patient received chemotherapy, endocrine therapy, and olaparib.
[b]ESR1 mutations in ctDNA at baseline were determined centrally using SafeSEQ Breast Cancer Panel (Sysmex Inostics, Baltimore, MD); ctDNA from 37 patients was available at the time of data cutoff for *ESR1* mutation evaluation.
CDK4/6, cyclin-dependent kinase 4/6; **ctDNA**, circulating tumor DNA; **ECOG**, Eastern Cooperative Oncology Group; ***ESR1***, estrogen receptor 1 gene.

Table 2. Patient disposition

Treatment status	Palazestrant dose 30 mg (n=3)	60 mg (n=3)	90 mg (n=3)	120 mg (n=37)	Total (N=46)
Treatment ongoing	0	2	2	18	22 (48)
Treatment discontinued	3	1	1	19	24 (52)
Reasons for treatment discontinuation					
Disease progression	3	1	1	13	18 (39)
Physician decision	0	0	0	3	3 (7)
Patient decision	0	0	0	2	2 (4)
Adverse event	0	0	0	1	1 (2)

Data shown are n or n (%).

Safety and Tolerability

- No DLTs were observed during the dose-escalation part of the study.
- Most treatment-emergent adverse events (TEAEs) were grade 1 or 2. (**Table 3**)
- There were no dose-related increases in incidence or severity of TEAEs.
- The most common TEAEs (≥20% of patients) included neutropenia, gastrointestinal events (nausea, vomiting, diarrhea, constipation), anemia, fatigue, and thrombocytopenia. (**Table 3**)

Table 3. Treatment-emergent adverse events 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	90 mg (n=3) All grades	90 mg (n=3) Grade ≥3	120 mg (n=37) All grades	120 mg (n=37) Grade ≥3	Total (N=46) All grades	Total (N=46) Grade 3	Total (N=46) Grade 4	Paloma-3[a,b] (N=345) All grades	Paloma-3[a,b] (N=345) Grade 3	Paloma-3[a,b] (N=345) Grade 4
Neutropenia[a]	2	2	3	2	3	2	32	27	40 (87)	28 (61)	5 (11)	96%[c]	56%[c]	11%[c]
Nausea	2	0	3	0	2	0	19	0	26 (57)	0	0	34%	0%	0%
Vomiting	1	0	2	0	2	0	12	0	17 (37)	0	0	19%	1%	0%
Anemia	2	0	0	0	1	0	9	1	12 (26)	1 (2)	0	30%	4%	0%
Diarrhea	1	0	1	0	0	0	9	0	11 (24)	0	0	24%	0%	0%
Constipation	1	0	2	0	0	0	7	1	10 (22)	1 (2)	0	-	-	-
Fatigue	2	0	0	0	0	0	8	1	10 (22)	1 (2)	0	41%	2%	0%
Thrombocytopenia	0	0	1	0	0	0	9	0	10 (22)	0	0	23%	2%	1%

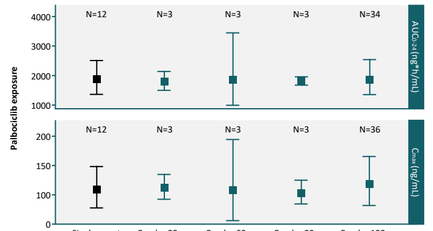
Data for the current study are shown as n or n (%).
[a]Combined term includes neutropenia and decreased neutrophil count.
[b]Adverse reactions reported in ≥10% of patients who received palbociclib plus fulvestrant in the PALOMA-3 study.[9]
[c]Reported as neutrophil count decreased in the laboratory abnormalities in the PALOMA-3 study.[9]
TEAE, treatment-emergent adverse event.

- One patient discontinued both drugs due to an AE of nausea concurrent with documented disease progression.
- No patients had dose reduction of palazestrant for neutropenia. Eleven patients had dose reduction of palbociclib for neutropenia.
- Neutropenia was reversible in all patients and the timing was consistent with the palbociclib-related neutropenia.[8,9]
  - One patient experienced neutropenia during Cycle 2 consistent with timing and duration of palazestrant-related neutropenia, which resolved. Patient subsequently discontinued treatment due to disease progression.

Pharmacokinetics

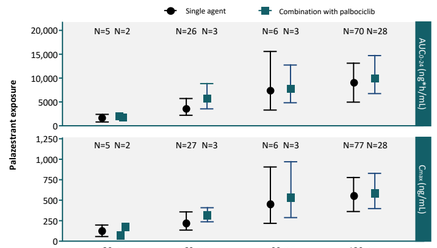
- There was no effect of palazestrant (30-120 mg) on palbociclib 125 mg exposure parameters.
- The combination therapy exposure parameters are comparable to published monotherapy exposure parameters. (**Figure 3**)
- $AUC_{[0\text{-}24]}$ and C_{max} ratios of combination therapy to monotherapy ranged from 96% to 107%.
- Palbociclib 125 mg did not affect palazestrant (30-120 mg) exposure parameters. The observed AUC_{024} and C_{max} were comparable to monotherapy exposure parameters. (**Figure 4**)

Figure 3. Steady-state exposure of palbociclib (125mg) in combination with palazestrant



Data are geometric mean ± geometric standard deviation.
AUCss,ss, area under the curve from 0 to 24 h; **Css,ss**, maximum concentration; **Combo**, combination.

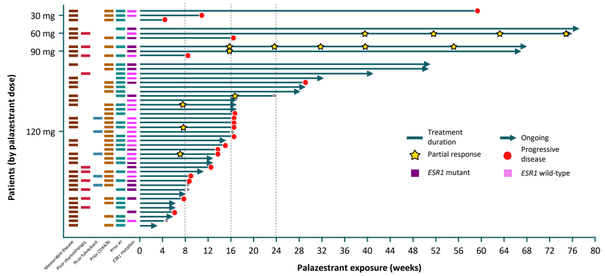
Figure 4. Steady-state exposure of palazestrant in combination with palbociclib



Data are geometric mean ± geometric standard deviation.
AUCss,ss, area under the curve from 0 to 24 h; **Css,ss**, maximum concentration.

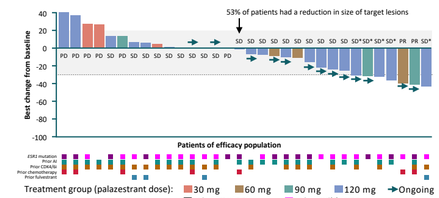
Efficacy

Figure 5. Duration of treatment[a]



[a]Each lane represents one patient.
[b]Two patients discontinued treatment due to patient decision; three discontinued due to physician decision.
AI, aromatase inhibitor; **CDK4/6i**, cyclin-dependent kinase 4/6 inhibitor; ***ESR1***, estrogen receptor 1 gene.

Figure 6. Best percent change from baseline in target lesions and best overall response



AI, aromatase inhibitor; **CDK4/6i**, cyclin-dependent kinase 4/6 inhibitor; ***ESR1***, estrogen receptor 1 gene; **PD**, progressive disease; **PR**, partial response (confirmed); **SD**, stable disease. *Indicates unconfirmed partial response (uPR)

- 5 patients remained on therapy >52 weeks. (**Figure 5**)
- Longest duration of treatment is 76 weeks and ongoing.
- Partial responses were observed in seven patients. (2 cPR; 5uPR)
- Clinical benefit rate was 46% (12/26 patients) in all patients and 60% (6/10) in patients with *ESR1* mutation in ctDNA at baseline.
- 53% of patients had any reduction in target lesion size. (**Figure 6**)
- Data are maturing; 22 patients (48%) remain on treatment.

Conclusions

- Palazestrant 120 mg in combination with palbociclib 125 mg was well tolerated.
  - Adverse event incidence and severity were consistent with the expected safety profile of palbociclib plus endocrine therapy and were similar to those reported previously.[8,9]
- No drug-drug interaction between palazestrant and palbociclib was observed, in agreement with previous reports.[8]
  - There was no induced metabolism or increase in exposure of either palbociclib or palazestrant when administered in combination.
- Tumor responses and prolonged disease stabilization were observed in this patient group, including in those previously exposed to CDK4/6 inhibitors.
- Findings from this study are consistent with previously reported data and support the ongoing clinical development of palazestrant in combination with CDK4/6 inhibitors for the treatment of ER+/HER2– MBC.

References

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