A Phase 1b/2 dose escalation and dose expansion study of OP-1250, an oral complete estrogen receptor antagonist (CERAN)/selective estrogen receptor degrader (SERD), in combination with the CDK4/6 inhibitor palbociclib in patients with advanced and/or metastatic estrogen receptor (ER)-positive, HER2-negative breast cancer (OP-1250-002; NCT05266105)

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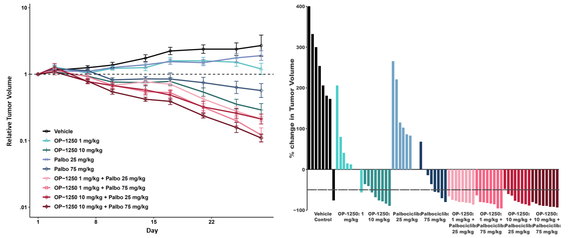
Background

- OP-1250 is a once-daily oral small molecule complete estrogen receptor antagonist (CERAN) and selective estrogen receptor degrader (SERD) that has displayed preclinical efficacy in a range of estrogen receptor–positive (ER+) breast cancer models, including xenograft models of *ESR1* mutant tumors and models of brain metastasis[1,2]
- In preclinical xenograft studies of both *ESR1* wild-type and mutant breast cancer models, the combination of OP-1250 and CDK4/6 inhibitors ribociclib or palbociclib resulted in improved antitumor efficacy and a greater than additive suppression of transcription associated with cell cycle progression[2] (**Figure 1**)
- Endocrine therapy in combination with the CDK4/6 inhibitor palbociclib improves progression-free survival in patients with ER+/ human epidermal growth factor receptor 2–negative (HER2-) advanced breast cancer[4]
- OP-1250-002 is a phase 1b/2 study investigating OP-1250 combined with palbociclib in patients with ER+/HER2- advanced breast cancer[5]
  - The recommended phase 2 dose (RP2D) of OP-1250 for monotherapy was established at 120 mg once-daily
  - OP-1250 monotherapy showed a favorable safety profile and robust antitumor activity in heavily pretreated patients
  - Clinical benefit was observed irrespective of baseline *ESR1* mutation status, demonstrating activity of OP-1250 in tumors with *ESR1* mutations known to be associated with endocrine resistance

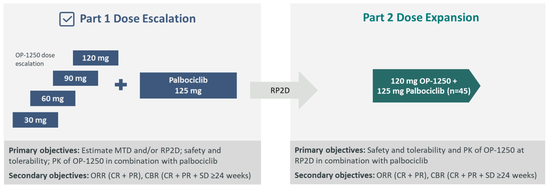
Figure 1. The combination of OP-1250 and CDK4/6 inhibitor palbociclib shrinks ER+ MCF7 xenografts[3]



Study Design

- Open-label phase 1 study of OP-1250 in combination with palbociclib 125 mg (**Figure 2**)
  - Dose escalation: 3 + 3 design, starting dose of OP-1250 30 mg + palbociclib 125 mg
  - Dose expansion: OP-1250 at the RP2D + palbociclib 125 mg
- OP-1250 administered once-daily and palbociclib administered once daily on days 1-21 of each 28-day treatment cycle
- In dose escalation, patients were monitored for dose-limiting toxicity (DLT) during Cycle 1
- Plasma PK samples for OP-1250 were obtained for all subjects on C1D1, C1D2, C1D8, C1D15, C2D15, C2D16, C3D1, C3D15, and C5, C7 and C9 on D1. Plasma PK samples for palbociclib were obtained on C1D15, C2D15, and C3D15

Figure 2. OP-1250-002 study schema



Key Inclusion Criteria:

- HR+ (defined as ER+ and either PR+ or PR-)/HER2- BC
- Evaluable disease (measurable or nonmeasurable) per RECIST 1.1
- 0-1 prior hormonal regimens or chemotherapy for locally advanced or metastatic disease
- CDK4/6 inhibitor naïve or pretreated

Definitions:

C, cycle; CBR, clinical benefit rate; CR, confirmed response; D, day; MTD, maximum tolerated dose; ORR, overall response rate; PK, pharmacokinetic; PR, partial response; RP2D, recommended phase 2 dose; SD, stable disease; WBC, white blood cell.

Results

Patient Population

- Data cutoff 12 September 2022
- 12 patients enrolled at 4 sites
- 4 cohorts (n=3 per cohort) OP-1250 dosed at 30, 60, 90, and 120 mg in combination with palbociclib 125 mg (**Tables 1 & 2**)
  - 10 of 12 patients received prior therapy for advanced disease, including 8 patients who had received prior CDK4/6 inhibitors
  - 9 patients received prior endocrine therapy for advanced disease

Table 1. Patient Disposition

Patients n (%)	30 mg (n=3)	60 mg (n=3)	90 mg (n=3)	120 mg (n=3)	Total (n=12)
Treatment ongoing	1	2	2	3	8 (67)
Treatment discontinued	2	1	1	0	4 (33)
Reasons for discontinuation: Radiographic Progression	2	1	1	0	4 (33)

Table 2. Demographics and Baseline Characteristics

Patient characteristics	Total (N=12)
Median age (years)	62
Range	49–76
ECOG performance status, n (%)	
0	9 (75)
1	3 (25)
Measurable disease at baseline, n (%)	11 (92)
Visceral disease (liver, lung, peritoneum, pleura, ascites), n (%)	6 (50)
Prior lines of therapy for advanced disease, n (%)	
0	2 (17)
1	7 (58)
2	2 (17)
3	1 (8)
Prior lines of endocrine therapy for advanced disease, n (%)	
0	3 (25)
1	9 (75)
Types of prior therapy for advanced disease, n (%)	
Chemotherapy	3 (25)
Aromatase inhibitor (AI)	8 (67)
Fulvestrant	1 (8)
CDK4/6 inhibitor	8 (67)
ESR1 mutations at baseline (ctDNA), n/N (%)	4 (36); N=11 evaluated

Safety

- No DLTs were observed during dose escalation and MTD was not reached
- Majority of TEAEs were grade 1 or 2 (**Table 3**)
  - Increasing dose did not show increase in frequency
  - Frequently reported TEAEs included nausea, neutropenia, vomiting, anemia, and gastroesophageal reflux disease (**Table 3**)

Table 3. Treatment-emergent Adverse Events Reported in ≥15% of Patients

	30 mg (n=3)		60 mg (n=3)		90 mg (n=3)		120 mg (n=3)		Total (N=12)	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥3	All grades	Grade ≥ 3
Neutropenia[a]	2	2	3	2	3	2	3	2	11 (92)	8 (67)
Nausea	2	0	1	0	1	0	2	0	6 (50)	0
Vomiting	1	0	2	0	1	0	1	0	5 (42)	0
Anemia	2	0	1	0	0	0	1	0	4 (33)	0
GERD	2	0	1	0	0	0	1	0	4 (33)	0
Constipation	1	0	1	0	0	0	1	0	3 (25)	0
Fatigue	2	0	0	0	0	0	1	1	3 (25)	1 (8)
Thrombocytopenia	0	0	1	0	0	0	2	0	3 (25)	0
COVID-19	0	0	2	0	0	0	0	0	2 (17)	0
Decreased appetite	1	0	0	0	0	0	1	0	2 (17)	0
Diarrhea	1	0	1	0	0	0	0	0	2 (17)	0
Headache	1	0	0	0	0	0	1	0	2 (17)	0
Sinus bradycardia	0	0	1	0	1	0	0	0	2 (17)	0
UTI	1	0	1	0	0	0	0	0	2 (17)	0
WBC count decreased	0	0	1	0	0	0	1	1	2 (17)	1 (8)

[a] Includes adverse events reported as either "Neutropenia" or "Neutrophil count decreased."
GERD, Gastroesophageal reflux disease; UTI, urinary tract infection, WBC, white blood cell.

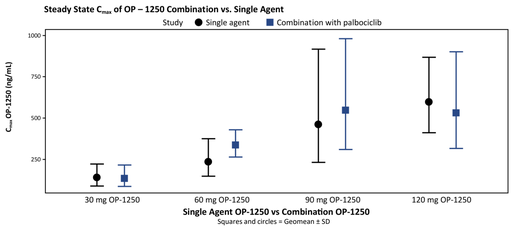
Safety (continued)

- No patients discontinued treatment due to adverse event, including neutropenia
- OP-1250 was not dose reduced in any patient
- Grade 3 neutropenia was reported in 8 patients (67%)
  - Time of onset was approximately 2-4 weeks on treatment
  - Palbociclib was dose reduced in three patients due to Grade 3 neutropenia
  - Four patients had a dose interruption of palbociclib due to Grade 3 neutropenia
  - Two patients had a dose interruption of both palbociclib and OP-1250 due to Grade 3 neutropenia
- No Grade 4 neutropenia was reported

Pharmacokinetics

- No drug-drug interaction between palbociclib and OP-1250 in the dose range of 30 to 120 mg
  - Palbociclib did not affect OP-1250 exposures compared to OP-1250 monotherapy (**Figure 3, Table 4**)
  - No effect of OP-1250 on palbociclib 125 mg exposures when compared to published concentrations (**Figure 4**)
  - Exposure of palbociclib was within 90% of reported geometric means values for palbociclib
- OP-1250 was readily bioavailable and demonstrated dose-proportional exposures and a long half-life
- Steady-state plasma levels show minimal peak-to-trough variability, enabling consistent inhibition of ER for the full dosing interval

Figure 3. Palbociclib did not affect OP-1250 exposures compared to OP-1250 monotherapy



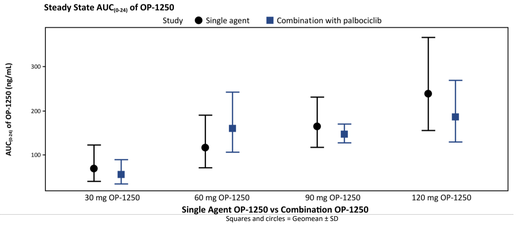
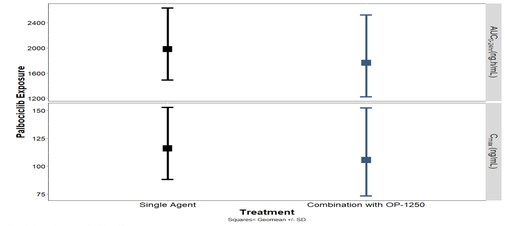


Table 4. OP-1250 PK in Combination With Palbociclib at Steady State

OP-1250 Dose	C_{min} (ng/mL)	C_{max} (ng/mL)	C_{avg} (ng/mL)	T_{max} (h)[a]	$AUC_{0\text{-}24}$ (ng*h/mL)
30 mg (n=2)	61.2 (37.8%)	136 (49.0%)	94.7 (12.9%)	2.0 (2.00-4.00)	2272 (12.9%)
60 mg (n=3)	186 (52.4%)	337 (24.2%)	253 (42.9%)	2.0 (2.00-4.00)	6068 (42.9%)
90 mg (n=3)	199 (55.3%)	549 (63.1%)	341 (48.8%)	2.0 (2.00-4.00)	8185 (48.8%)
120 mg (n=3)	254 (71.7%)	532 (56.0%)	361 (56.3%)	4.0 (2.00-6.00)	8675 (56.3%)

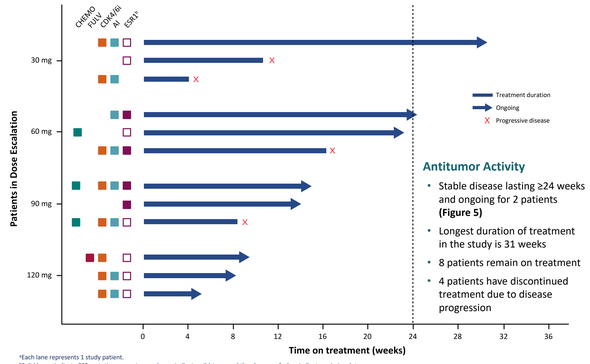
Geomean (Geo %CV) Presented
[a]Median (Min-Max)

Figure 4. No effect of OP-1250 on palbociclib 125 mg exposures when compared to published concentrations[a]



[a]Figure includes all doses of OP-1250. N=12 patients.

Figure 5. Duration of treatment[a]



[a]Each lane represents 1 study patient.
[b]Solid boxes indicate ESR mutation present, open boxes indicate wild-type, and the absence of a box indicates missing data.
AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CHEMO, chemotherapy; ESR1, estrogen receptor 1; FULV, fulvestrant.

Antitumor Activity

- Stable disease lasting ≥24 weeks and ongoing for 2 patients (**Figure 5**)
- Longest duration of treatment in the study is 31 weeks
- 8 patients remain on treatment
- 4 patients have discontinued treatment due to disease progression

Conclusions

- The combination of OP-1250 up to 120 mg with palbociclib 125 mg is safe and well-tolerated
- No drug-drug interaction (DDI) has been observed
- No induced metabolism of palbociclib dosed in combination with OP-1250 has been observed
- Exposure of OP-1250 in combination with palbociclib is consistent with the observed monotherapy OP-1250 exposure levels
- No dose-related increase in the incidence or severity of adverse events was observed
- Neutropenia events observed are consistent with the expected profile of palbociclib plus letrozole (PALOMA 2[6] – overall incidence of neutropenia was 80% with 56% grade 3 and 10% grade 4)
- The overall safety profile, absence of MTD, and consistent drug exposure support OP-1250 at a dose of 120 mg as the RP2D in combination with palbociclib 125 mg
- Enrollment in the dose expansion is ongoing at the RP2D of OP-1250 120 mg in combination with palbociclib 125 mg

References

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