Preliminary phase 1/2 results from OP-1250-001, a study of OP-1250, an oral CERAN/SERD, in patients with advanced and/or metastatic estrogen receptor-positive, HER2-negative breast cancer (NCT04505826)

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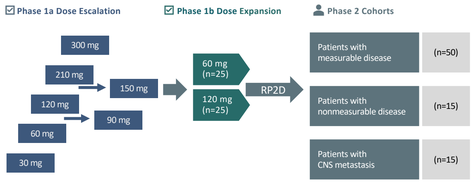
Background

- OP-1250 is an oral CERAN (complete estrogen receptor antagonist)/SERD (selective estrogen receptor degrader) that has demonstrated anti-tumor efficacy in a range of preclinical xenograft models of breast cancer, including in ***ESR1*** and ***PIK3CA*** mutations and central nervous system (CNS) metastasis[1,2]
- Phase 1a dose escalation[3]:
  - OP-1250 was administered at escalating doses from 30 mg to 300 mg; maximum tolerated dose (MTD) was not reached, and no dose limiting toxicities (DLTs) were observed
  - Pharmacokinetics (PK) demonstrated high oral bioavailability, with dose-proportional exposures and long half-life ($t_{1/2}$ ~ 8 days), supporting once-daily dosing
  - Efficacy was observed in heavily pretreated patients with 2 confirmed partial responses at 60 mg and 120 mg
  - OP-1250 doses of 60 mg and 120 mg were selected based on PK, tolerability, and initial efficacy for further evaluation in the dose-expansion cohort
- Preliminary results from phase 1a dose escalation and phase 1b dose expansion at OP-1250 doses of 60 mg and 120 mg are presented

Methods

- OP-1250-001 (NCT04505826) is a first-in-human, phase 1/2 study of once-daily oral dose of OP-1250 in adults with advanced and/or metastatic estrogen receptor (ER)-positive, HER2-negative breast cancer (**Figure 1**)

Figure 1. OP-1250-001 First-in-Human Phase 1/2 Monotherapy Trial: Study Design



Primary objectives: pharmacokinetics, safety and tolerability, identify RP2D

Secondary objectives: ORR (CR + PR), CBR (CR + PR + SD ≥24 weeks)

Objectives: antitumor activity in measurable-disease cohort, safety and tolerability at RP2D

CBR includes patients who received at least 1 cycle of treatment, had at least 1 postbaseline tumor assessment evaluable for a response, and enrolled ≥24 weeks prior to the data cut-off date. CBR, clinical benefit rate; CNS, central nervous system; CR, confirmed response; ORR, overall response rate; PR, partial response; RP2D, recommended phase 2 dose; SD, stable disease

Table 1. Key Inclusion Criteria for Phase 1

Phase	Inclusion Criteria
Phase 1a	• Tumor must be ER+/HER2– • At least 1 prior hormone-based therapy for locally advanced, recurrent, or metastatic disease • 0 to 2 prior chemotherapy regimens for locally advanced or metastatic disease • Measurable and nonmeasurable disease (evaluable disease)
Phase 1b	• Tumor must be ER+/HER2– • 1 to 4 prior hormone-based therapies for locally advanced, recurrent, or metastatic disease • 0 to 1 prior chemotherapy regimen for locally advanced or metastatic disease • Measurable disease by Response Evaluation Criteria in Solid Tumors 1.1 criteria

References

1. Hodges-Gallagher L, et al. EORTC-NCI-AACR 2020 Meeting. Poster #193.
2. Hodges-Gallagher L, et al. AACR Annual Meeting 2021. Poster #LB122.
3. Patel M, et al. San Antonio Breast Cancer Symposium 2021. Poster #P1-17-12.

Acknowledgments

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Results

Patient Population

- Data cut-off date for this analysis was 2 September 2022
- A total of 68 patients were treated (**Tables 2 and 3**):
  - 82% had visceral disease at baseline
  - 61% had ≥2 prior lines of endocrine therapy in the advanced setting
  - 96% received prior cyclin-dependent kinase 4/6 (CDK4/6) inhibitor
  - 65% received prior fulvestrant
  - 32% received prior chemotherapy in the advanced setting
  - 59% had an ESR1 mutation at baseline

Table 2. Patient Disposition

Patients, n (%)	60 mg (n=33)	120 mg (n=35)	Total (N=68)
Currently on treatment	10	11	21 (31)
Treatment discontinued	23	24	47 (69)
Reasons for discontinuation:			
Radiographic Progression	19	16	35 (50)
Clinical Progression	2	5	7 (12)
Toxicity[a]	0	2	2 (3)
Other[b]	2	1	3 (4)

[a]Grade 3 INR increase (not related); Grade 4 neutropenia (related)
[b]HER2– disease in post-treatment biopsy; Patient withdrew consent; Grade 3 large intestinal obstruction related to disease progression (120 mg)

Table 3. Demographics and Baseline Disease Characteristics

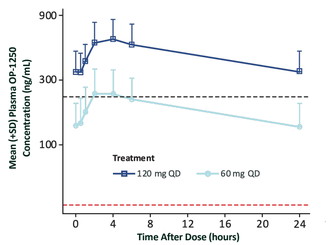
Patient characteristics	60 mg (n=33)	120 mg (n=35)	Total[a] (N=68)
Age, median, years	61	61	61
Range	30–81	39–77	30–81
Menopausal status (female), n (%)			
Postmenopausal	29 (88)	32 (91)	61 (90)
Peri-/premenopausal	4 (12)	3 (9)	7 (10)
ECOG performance status, n (%)			
0	22 (67)	17 (49)	39 (57)
1	11 (33)	18 (51)	29 (43)
Measurable disease at baseline, n (%)	32 (97)	34 (97)	66 (97)
Visceral disease (liver, lung, peritoneum, pleura, ascites), n (%)	27 (82)	29 (83)	56 (82)
Prior lines of therapy in advanced setting, n (%)			
1	9 (27)	11 (31)	20 (29)
2	9 (27)	10 (29)	19 (28)
≥3	15 (46)	13 (37)	28 (41)
Missing	0	1 (3)	1 (2)
Prior lines of endocrine therapy in advanced setting, n (%)			
1	13 (39)	12 (34)	25 (36)
2	8 (24)	15 (43)	23 (34)
≥3	11 (33)	7 (20)	18 (27)
Missing	1 (3)	1 (3)	2 (3)
Types of prior therapy in advanced setting, n (%)			
Chemotherapy	14 (42)	8 (23)	22 (32)
AI	26 (79)	29 (83)	55 (81)
Fulvestrant	22 (67)	22 (63)	44 (65)
CDK4/6 inhibitor	32 (97)	33 (94)	65 (96)
ESR1 mutations at baseline (ctDNA), n/N (%)	15/20 (75)	12/26 (46)	27/46 (59)

[a]Sums may not total to 100% due to rounding.
AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinase 4/6; ECOG, Eastern Cooperative Oncology Group.

Pharmacokinetics

- OP-1250 is characterized by high oral bioavailability, relatively fast absorption, and dose proportional exposure (**Table 4**)
- Mean terminal half-life ($t_{1/2}$)=8 days, supporting once-daily dosing
- Steady-state plasma levels showed minimal peak-to-trough variability, allowing complete inhibition of the ER for the full dosing interval (**Figure 2**)
- Dosing at the RP2D (120 mg once daily [QD]) yields drug exposure that exceeds the predicted efficacious threshold based on the estradiol-supplemented preclinical models

Figure 2. OP-1250 Steady-state Plasma Concentration-time Profiles: C2D1 Phase 1a Dose Escalation and Phase 1b Dose Expansion Combined



Dashed black lines=target efficacious exposure based on estradiol-supplemented preclinical models (C_{min}=226 ng/mL) (8 studies); dotted red line=target efficacious exposure based on preclinical models without estradiol supplementation (C_{min}=36 ng/mL). C, cycle; D, day; QD, once daily.

Table 4. OP-1250 Steady-state PK: C2D1 Phase 1a Dose Escalation and Phase 1b Dose Expansion Combined[a]

OP-1250 daily dose	C_{min} (ng/mL)[b]	C_{max} (ng/mL)[b]	t_{max} (h)[c]	C_{avg} (ng/mL)[b]	$AUC_{0\text{-}24}$ (ng*h/mL)[b]
60 mg n=25	122 (52.2)	237 (48.2)	4.00 (1.00–6.00)	168 (47.2)	4026 (47.2)
120 mg n=26	319 (43.2)	598 (38.2)	4.00 (2.00–6.00)	430 (38.7)	10330 (38.7)

[a]19 September 2022 data cut-off date. [b]Geometric Mean (GeoCV%) presented, unless otherwise noted. [c]Median (min-max). C, cycle; D, day; PK, pharmacokinetics.

Safety

Treatment-Emergent Adverse Events (TEAEs)

- Treatment with OP-1250 was well tolerated at 60- and 120-mg dose levels (N=68)
- The most common TEAEs at 60 mg and 120 mg that occurred in at least 15% of patients were nausea, fatigue, vomiting, and headache (**Table 5**)
- 3 patients had a grade 3 event assessed as related to study drug: anemia (60 mg), nausea (120 mg), and fatigue (120 mg)
- 1 patient's dose was reduced due to a related AE of grade 1 upper abdominal pain at 120 mg
- 1 patient had a grade 5 AE of disease progression at 60 mg assessed as not study drug related

Neutropenia AEs

- Events of grade 3/4 neutropenia have been observed, occurring approximately 4–6 weeks into therapy and have been reversible
- 1 patient had grade 3 neutropenia at 120 mg and was discontinued due to concurrent disease progression with recovery of neutropenia
- 3 patients had grade 4 neutropenia at 120 mg:
  - 1 patient's dose was interrupted for 1 week and was restarted at a lower dose (60 mg) with a subsequent cPR and no further neutropenia
  - 1 patient had grade 4 neutropenia concurrent with disease progression and was discontinued from treatment and recovered
  - 1 patient had febrile neutropenia with no evidence of infection, was discontinued from treatment, and recovered

Table 5. TEAEs Occurring in ≥15% of Patients

	60 mg (n=33)			120 mg (n=35)			Total (N=68)	
TEAEs in ≥15% of patients	Grade 1	Grade 2	Grade ≥3	Grade 1	Grade 2	Grade ≥3	All grades	Grade ≥3
Patients with ≥1 event (highest grade), n	10	13	4	14	8	10	59 (87%)	14 (21%)
Nausea, n	11	3	0	19	1	2	36 (53%)	2 (3%)
Fatigue, n	8	4	0	5	2	2	21 (31%)	2 (3%)
Vomiting, n	4	1	0	7	0	2	14 (21%)	2 (3%)
Headache, n	5	0	0	7	0	0	12 (18%)	0

TEAE, treatment-emergent adverse event.

Efficacy

- 4 confirmed and 2 unconfirmed partial responses have been observed with a clinical benefit rate of 29% (**Tables 6 and 7**)
- 4 patients remained on therapy >52 weeks; 2 of these had durable confirmed responses (**Figure 3**)
- 41% of patients had any reduction in target lesion size (**Figure 4**)

Table 6. Efficacy Response by Cohort in the Anticipated RP2D Range[a,b]

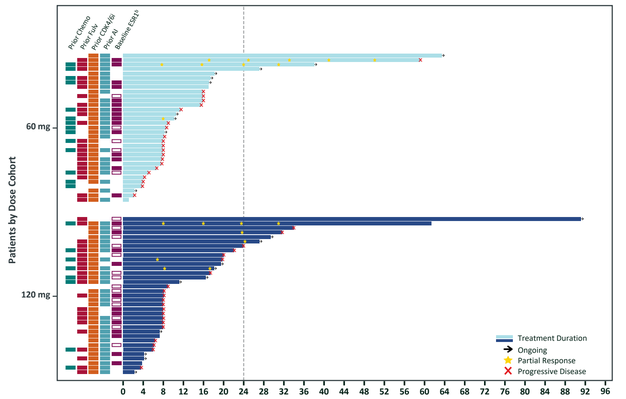
	Dose cohort		
Efficacy parameter	60 mg (n=28)	120 mg (n=29)	Total (n=57)
uPR, n	1	1	2
cPR, n	2	2	4
SD ≥24 weeks, n	2	4	6
CBR (cCR+cPR+SD ≥24 weeks), n/N (%)	4/16 (25)	6/18 (33)	10/34 (29)

Table 7. Efficacy Response by Cohort in the Anticipated RP2D Range in Patients With ESR1 Mutation[a,b]

	Dose cohort		
Efficacy parameter	60 mg (n=13)	120 mg (n=9)	Total (n=22)
uPR, n	1	0	1
cPR, n	2	1	3
SD ≥24 weeks, n	0	1	1
CBR (cCR+cPR+SD ≥24 weeks), n/N (%)	2/8 (25)	2/6 (33)	4/14 (29)

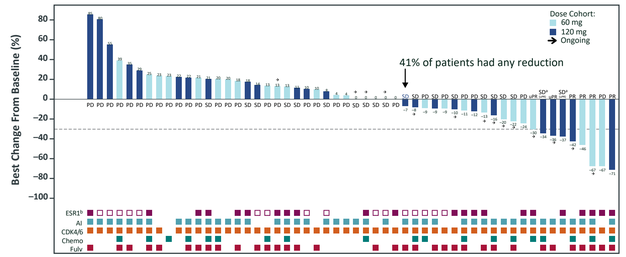
[a]uPR, cPR, SD, and CBR were evaluated per RECIST version 1.1.
[b]Includes patients who received at least 1 cycle of treatment and had at least 1 postbaseline tumor assessment evaluable for a response.
CBR includes patients who received at least 1 cycle of treatment, had at least 1 postbaseline tumor assessment evaluable for a response, and enrolled ≥24 weeks prior to the data cut-off date. CBR, clinical benefit rate; cCR, confirmed complete response; cPR, confirmed partial response; RP2D, recommended phase 2 dose; SD, stable disease; uPR, unconfirmed partial response.

Figure 3. 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; Fulv, fulvestrant; PD, progressive disease; PR, partial response.

Figure 4. Best Percent Change From Baseline in Target Lesions and Best Overall Response



[a]Patient had an unconfirmed partial response and later progressed at a subsequent scan.
[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; Fulv, fulvestrant; PD, progressive disease; PR, partial response; QD, once daily; SD, stable disease; uPR, unconfirmed partial response.

Conclusions

- OP-1250 completely blocks transcriptional activity of both wild-type and mutant ER
- OP-1250 was well tolerated with drug exposure supporting once oral daily dosing
  - The majority of TEAEs were Grade 1 or 2
  - At 120 mg QD, exposures exceeded the preclinical efficacy threshold and achieved exposure levels approximately 20x that of fulvestrant
- 4 confirmed and 2 unconfirmed responses have been observed in heavily pretreated patients, including patients who received prior fulvestrant. Efficacy data continues to mature
  - 4 patients remained on therapy >52 weeks; 2 of these had durable confirmed responses
  - Evidence of activity was observed in patients with both wild type and ESR1 mutations
- The overall safety profile, absence of MTD, drug exposure and PK profile, and the preliminary anti-tumor activity support 120 mg OP-1250 QD as the RP2D
- Further clinical development of OP-1250 includes:
  - Ongoing Phase 2 monotherapy expansion cohorts (NCT04505826)
  - Phase 1b study of OP-1250 in combination with palbociclib (NCT05266105)
    - Preliminary data in combination with palbociclib will be presented in late 2022
  - Phase 1b study of OP-1250 in combination with either ribociclib or alpelisib (NCT05508906)
- A Phase 3 monotherapy 2nd/3rd line study is planned for mid-2023

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