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Results from the phase 1/2 study of OP-1250, an oral complete estrogen receptor (ER) antagonist (CERAN) and selective ER degrader (SERD) in patients (pts) with advanced or metastatic ER-positive, HER2-negative breast cancer

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DECLARATION OF INTERESTS

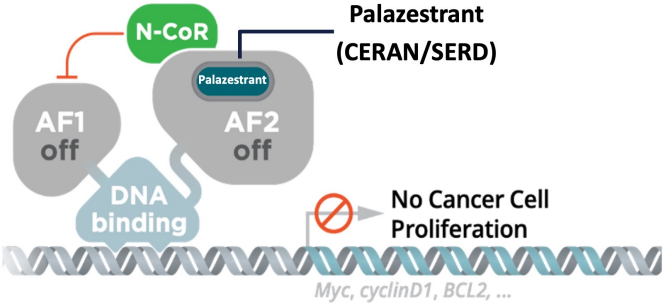
Nancy U. Lin

Institutional Research Support: Genentech, Pfizer, Merck, Seattle Genetics, Zion Pharmaceuticals, Olema Pharmaceuticals, AstraZeneca

Consulting Honoraria: Puma, Seattle Genetics, Daichii-Sankyo, AstraZeneca, Denali Therapeutics, Prelude Therapeutics, Olema Pharmaceuticals, Aleta BioPharma, Affinia Therapeutics, Voyager Therapeutics, Janssen, Blueprint Medicines, Stemline/Menarini, Artera Inc., Reverie Labs

Palazestrant (OP-1250) Is An Oral CERAN/SERD

- Palazestrant (OP-1250) is an oral complete ER antagonist (CERAN) and selective ER degrader (SERD)
- Palazestrant potently binds and completely blocks transcriptional activity of both wild-type and *ESR1*-mutant ER[1,2]
- Palazestrant was well tolerated through dose escalation, at doses up to 300 mg/day, with no dose-limiting toxicities and MTD was not reached[1]



- Palazestrant has highly favorable pharmacokinetics, oral bioavailability with once-daily dosing, and mean terminal half-life of 8 days
- **Here we present results for patients treated at the palazestrant RP2D of 120 mg QD**

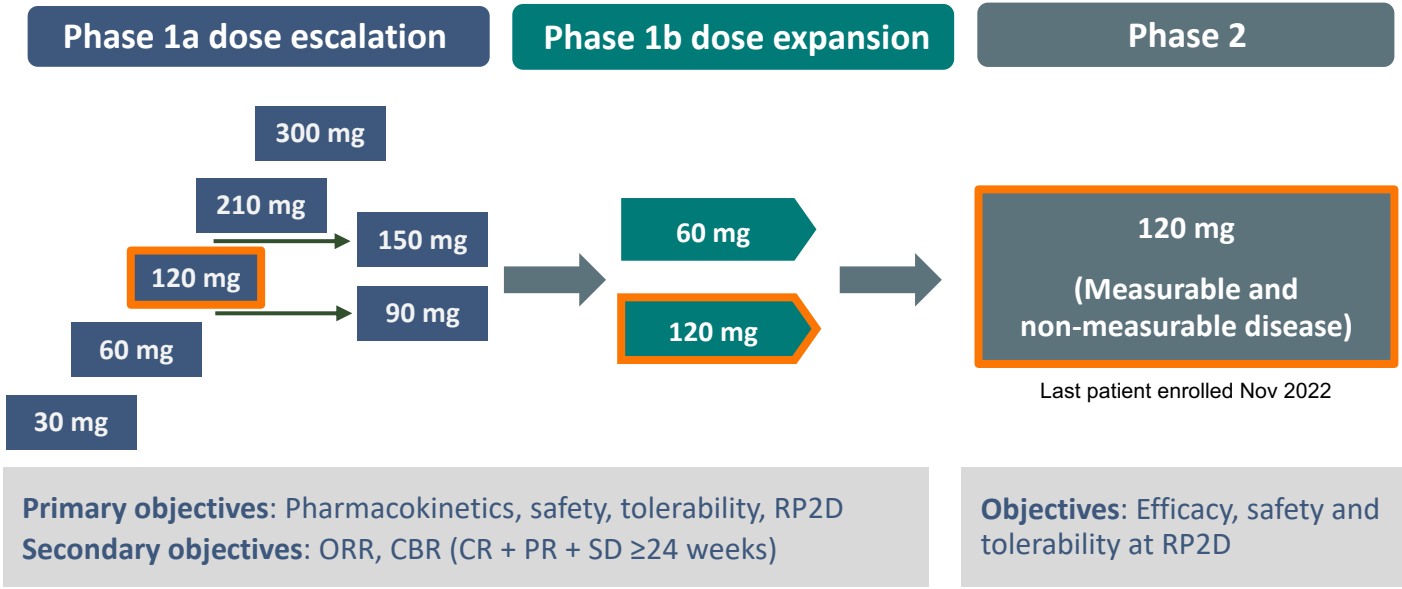
Abbreviations: **AF**, activation function; **CERAN**, complete oestrogen receptor antagonist; **ER**, estrogen receptor; ***ESR1***, oestrogen receptor 1 gene; **MTD**, maximum tolerated dose; **N-CoR**, nuclear receptor corepressor; **QD**, once daily; **RP2D**, recommended phase 2 dose; **SERD**, selective oestrogen receptor degrader.

References: 1. Alemany C, et al. AACR-NCI-EORTC Molecular Targets and Cancer Therapeutics Symposium; October 7–10, 2021. Abstract P037; 2. Parisian A, et al. San Antonio Breast Cancer Symposium 2022. Poster #P2-24-07.

First-in-Human Phase 1/2 Trial of Palazestrant

Key Phase 2 Eligibility Criteria*

- ER+/HER2-negative advanced breast cancer
- 1–4 prior endocrine therapies for metastatic disease
- Up to 1 line of prior chemotherapy for metastatic disease
- Measurable or non-measurable disease by RECIST v1.1



*Phase 1a dose escalation allowed patients with at least 1 prior line of endocrine therapy and up to 2 prior lines of chemotherapy for metastatic disease.

Abbreviations: **CBR**, clinical benefit rate; **CR**, complete response; **ER+**, estrogen receptor-positive; **HER2**, human epidermal growth factor receptor 2; **ORR**, overall response rate; **PR**, partial response; **RECIST**, Response Evaluation Criteria in Solid Tumours; **RP2D**, recommended phase 2 dose; **SD**, stable disease.

Demographics: Heavily Pretreated Patient Population

Characteristics	120 mg palazestrant N=86*
Age, median, years (range)	61 (32-85)
Pre- or peri-menopausal, n (%)	7 (8)
ECOG performance status, n (%)	
0	46 (54)
1	40 (47)
Measurable disease at baseline, n (%)	69 (80)
Visceral disease (liver, lung, peritoneum, pleura, ascites), n (%)	61 (71)
Prior lines of therapy in advanced setting, n (%)	
1	21 (24)
2	29 (34)
3	19 (22)
4+	17 (20)
Prior lines of endocrine therapy in advanced setting, n (%)	
1	30 (35)
2	32 (37)
3	15 (17)
4+	9 (10)
Types of prior therapy in advanced setting, n (%)	
CDK4/6 inhibitor	83 (97)
Aromatase inhibitor	73 (85)
Fulvestrant	57 (66)
Chemotherapy	27 (31)
mTOR inhibitor	25 (29)
ESR1 mutations at baseline (ctDNA), n/N (%)	36/75 (48)

- **42% of patients received ≥3 prior lines of systemic therapy for metastatic disease**
- 65% with ≥2 prior lines of endocrine therapy
- 80% measurable disease
- 71% visceral disease
- 97% prior CDK4/6 inhibitor
- 66% prior fulvestrant
- 31% prior chemotherapy
- 48% *ESR1* activating mutations

*Includes patients from phase 1 (dose escalation and dose expansion) and phase 2 at 120 mg, and 3 patients whose dose was increased from 60 to 120 mg early in treatment.

Abbreviations: **CDK4/6**, cyclin dependent kinase 4/6; **ECOG**, Eastern Cooperative Oncology Group; ***ESR1***, estrogen receptor 1 gene; **mTOR**, mammalian target of rapamycin.

Safety: Most AEs were Grade 1/2

Treatment-emergent AEs in ≥15% of patients	120 mg palazestrant N=83				
	Grade 1	Grade 2	Grade 3	Grade 4	All n (%)
Nausea	47	4	3	0	54 (65)
Vomiting	19	2	4	0	25 (30)
Fatigue	13	6	3	0	22 (27)
Neutropenia	6	6	3	6	21 (25)
Headache	16	1	0	0	17 (20)
Constipation	13	2	0	0	15 (18)
AST increased	10	2	1	0	13 (16)

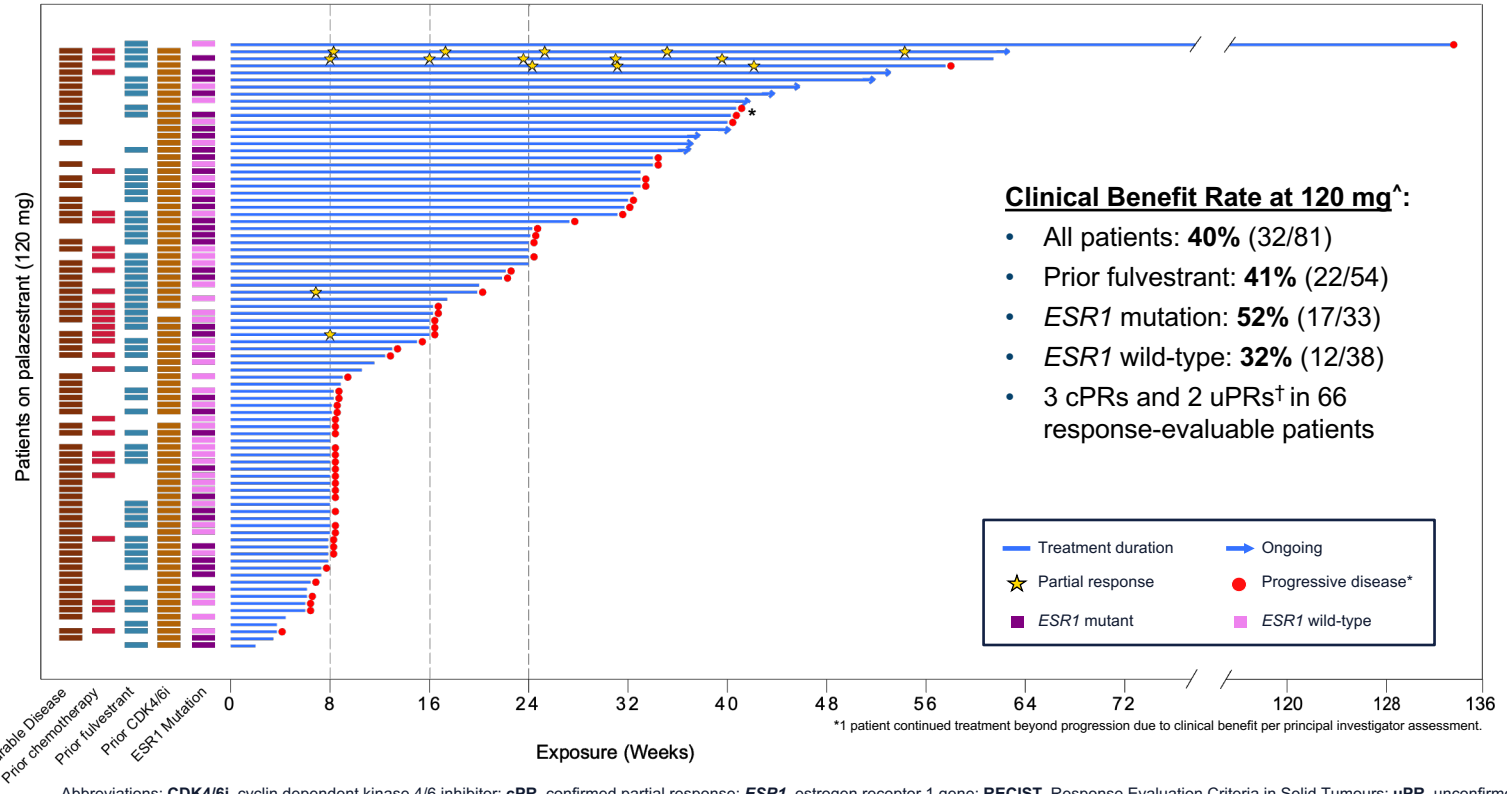
- Less than 6% of patients discontinued due to a treatment-related adverse event
- Grade 4 neutropenia in 6 patients, at approximately 4–6 weeks
  - 3 dose interruptions with recovery and dose reduction (2 pt to 90 mg, 1 to 60 mg) without recurrence of neutropenia
  - 3 had dose discontinuation followed by recovery
  - No increase in neutropenia in combination with palbociclib[1]

Abbreviations: **AE**, adverse event; **AST**, aspartate aminotransferase.

References: 1. Chan A, et al. Presented at ESMO Breast Annual Congress. May 11−15, 2023. Abstract: 202P

Clinical Benefit Rate: 40% Overall; 52% with *ESR1* Mutation

Treatment duration (weeks) and response per RECIST v1.1 by dose in all patients (N=86) as of July 7, 2023



*1 patient continued treatment beyond progression due to clinical benefit per principal investigator assessment.

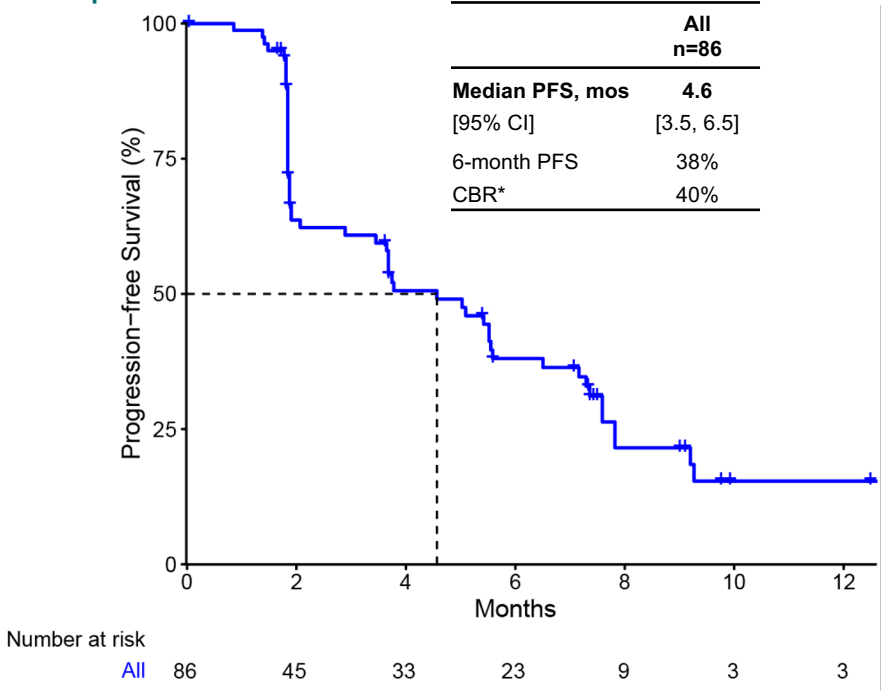
†Unconfirmed due to disease progression at a subsequent scan.

^Clinical benefit rate is the proportion of patients who remained on treatment through at least 24 weeks with a confirmed CR or PR, or stable disease. The CBR analysis includes patients who received at least one evaluable postbaseline radiographic assessment.

Abbreviations: **CDK4/6i**, cyclin dependent kinase 4/6 inhibitor; **cPR**, confirmed partial response; ***ESR1***, estrogen receptor 1 gene; **RECIST**, Response Evaluation Criteria in Solid Tumours; **uPR**, unconfirmed partial response.

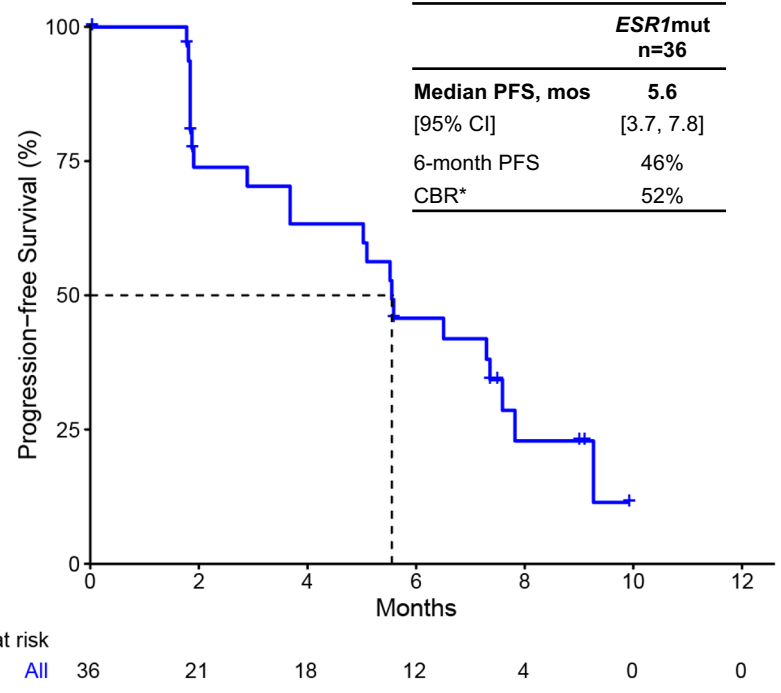
Median PFS: 4.6 mos Overall and 5.6 mos with *ESR1* Mutations

All patients



	All n=86
Median PFS, mos	**4.6**
[95% CI]	[3.5, 6.5]
6-month PFS	38%
CBR*	40%

Patients with *ESR1* mutation

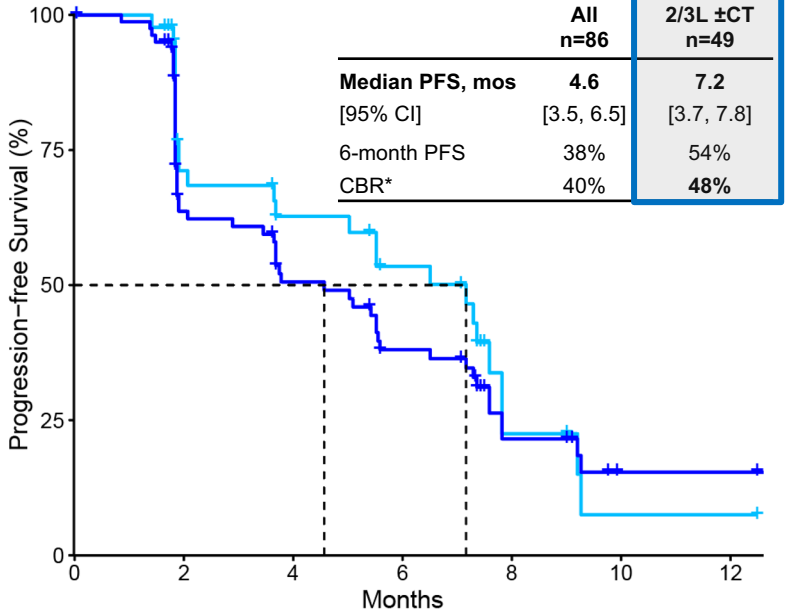


	*ESR1*mut n=36
Median PFS, mos	**5.6**
[95% CI]	[3.7, 7.8]
6-month PFS	46%
CBR*	52%

Abbreviations: **2/3L**, second/third line; **± CT**, plus/minus chemotherapy; **CBR**, clinical benefit rate; **CI**, confidence interval; ***ESR1***, estrogen receptor 1 gene; **mos**, months; **mut**, mutation; **NA**, not applicable; **PFS**, progression-free survival as assessed by RECIST v1.1.
*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.

Median PFS in 2/3L: 7.2 mos Overall and 7.3 mos with *ESR1* Mutations

All patients

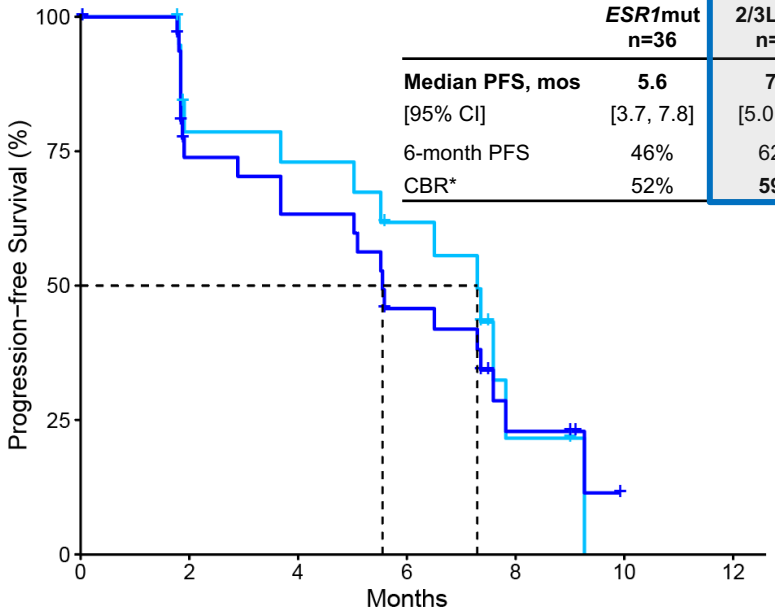


	All n=86	2/3L ±CT n=49
Median PFS, mos	**4.6**	**7.2**
[95% CI]	[3.5, 6.5]	[3.7, 7.8]
6-month PFS	38%	54%
CBR*	40%	**48%**

Number at risk

All	86	45	33	23	9	3	3
2/3L ±CT	49	26	21	16	4	1	1

Patients with *ESR1* mutation



	*ESR1*mut n=36	2/3L ±CT n=23
Median PFS, mos	**5.6**	**7.3**
[95% CI]	[3.7, 7.8]	[5.0, NA]
6-month PFS	46%	62%
CBR*	52%	**59%**

Number at risk

All	36	21	18	12	4	0	0
2/3L ±CT	23	14	13	10	2	0	0

Abbreviations: **2/3L**, second/third line; **± CT**, plus/minus chemotherapy; **CBR**, clinical benefit rate; **CI**, confidence interval; ***ESR1***, estrogen receptor 1 gene; **mos**, months; **mut**, mutation; **NA**, not applicable; **PFS**, progression-free survival as assessed by RECIST v1.1.
*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.

Conclusions

- Palazestrant (OP-1250) 120 mg QD was well tolerated and demonstrated efficacy in heavily pretreated patients, including tumor responses and prolonged disease stabilization in those previously exposed to CDK4/6 inhibitors and multiple lines of endocrine therapy
  - Median PFS 4.6 mos and CBR 40% for all patients
  - Median PFS 5.6 mos and CBR 52% with *ESR1* mutation
  - In 2/3L, median PFS 7.2 mos and CBR 48% overall; PFS 7.3 mos and CBR 59% with *ESR1* mutation
- These results support further investigation of palazestrant in ER+ MBC
  - A phase 3 study of palazestrant monotherapy vs. standard of care in 2/3L ER+/HER2- MBC is ongoing (OPERA-01; NCT06016738)
  - Phase 1/2 studies of palazestrant with the CDK4/6 inhibitors palbociclib and ribociclib, and with the Pi3Ka inhibitor alpelisib, are ongoing (NCT05266105, NCT05508906)

Abbreviations: **2/3L**, second/third line; **± CT**, plus/minus chemotherapy; **CBR**, clinical benefit rate; **CDK4/6**, cyclin dependent kinase 4/6; **ER+**, estrogen receptor-positive; ***ESR1***, estrogen receptor 1 gene; **HER2**, human epidermal growth factor receptor 2; **MBC**, metastatic breast cancer; **PFS**, progression-free survival; **QD**, once daily.

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