Aspiring to Improve the Lives of Women with Breast Cancer

January 2023
Forward-Looking Statements

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Leading the Next Generation of Oral CERAN/SERDs for the Treatment of ER+/HER- Metastatic Breast Cancer (MBC)

**OP-1250, Best-in-Class CERAN/SERD for ER+/HER2- MBC**
- Completely shuts down estrogen receptor signaling pathways in women with ER+/HER2- MBC
- Internally-discovered, wholly-owned IP with no royalty burden

**Clinical Validation as a Monotherapy and in Combo w/ CDK4/6i**
- Over 160 patients treated to date with OP-1250
- Highly encouraging Phase 1/2 clinical results in both monotherapy and combination studies

**Initiating 1st Pivotal Phase 3 monotherapy study in mid-2023**
- FDA Fast Track designation in 2L+ ER+/HER2- MBC
- Combination studies ongoing with Ibrance®, Kisqali® and Piqray®

**Multi-Billion Dollar Commercial Market Opportunity**
- 2L/3L+ MBC, represents a $3-5B commercial opportunity
- 1L MBC in combination with CDK 4/6i, represents a $5-10B commercial opportunity

Strong cash position of $222.6M\(^{(1)}\) to support clinical development and operations into 2H 2024

\(^{(1)}\) As of September 30, 2022.
### Rapidly Advancing OP-1250 into Pivotal Studies Studies Beginning in 2023

#### Evaluating OP-1250 across a range of ER cohorts in monotherapy and combination trials

<table>
<thead>
<tr>
<th>ER+/HER2- Metastatic Breast Cancer</th>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Planned Next Steps</th>
</tr>
</thead>
<tbody>
<tr>
<td>2/3 Line Monotherapy (with and without CNS metastases)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Phase 3 initiation mid-2023</td>
</tr>
<tr>
<td>Combo Therapy with CDK 4/6i palbociclib</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Phase 2 expansion ongoing</td>
</tr>
<tr>
<td>Combo Therapy with CDK 4/6i ribociclib</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Phase 1b dose escalation ongoing</td>
</tr>
<tr>
<td>Combo Therapy with PI3Kα alpelisib with PIK3CA mutated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Phase 1b dose escalation ongoing</td>
</tr>
<tr>
<td>Combo Therapy with other agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ER+/HER2+ Metastatic Breast Cancer with CNS METS</th>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Planned Next Steps</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combo Therapy with CNS metastases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MBC = metastatic breast cancer; PI3Kα = phosphatidylinositol 3-kinase alpha; CDK4/6i = CDK4/6 inhibitor

(1) Patient population may be studied as additional cohort(s) of current Phase 1/2 clinical trial or may be studied in a separate clinical trial.
Breast Cancer is the Second Most Common Diagnosed Cancer Worldwide

In 2022, approximately **288K**
Women in the U.S. were diagnosed with breast cancer

**43,250**
Women in the U.S. will succumb to metastatic breast cancer

**Majority of All Breast Cancers express Estrogen Receptor (ER+)**
- **73%** HR+ / HER2-
- **12%** HR- / HER2-
- **11%** HR+ / HER2+

**Current Endocrine Therapy Options**
**SERMs, AIs, SERDs**

Limitations include:
- Incomplete ER antagonism
- Sub-optimal PK profile
- Limited CNS penetration
- Tolerability issues

**Better ER targeting agents are needed**

References: World Health Organization; American Cancer Society. Facts and Figures 2022; SEER database
Endocrine Therapy Remains the Backbone of ER+ Breast Cancer Treatment

**OP-1250 has the potential to improve upon existing treatments to become the best-in-class ET**

Illustrative Examples of ER+/HER2- Breast Cancer Treatment Options

**OP-1250**

OP-1250 has the potential to be used across multiple lines of treatment

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**2nd/3rd LINE +: ~2-12+ months of therapy**

- **Oral CERAN/SERDs (emerging)**
- **Fulvestrant (CERAN/SERD)**
- **AI**
- **Tam (SERM)**
- **PI3Ki ³ +/- Fulv (CERAN/SERD)**
- **AI +/- mTORi ⁴**
- **Chemo***

Physician choice of one of the above options based on patient characteristics, tumor biology, prior therapy and response to prior therapy and whether there is a need for chemo

**1st Line: ~6-36+ months of therapy**

- **Oral CERAN/SERDs + CDK4/6i**
- **AI + CDK4/6i²**
- **Fulvestrant (CERAN/SERD) + CDK4/6i²**
- **Chemo***

Physician choice of one of the above options based on patient characteristics, tumor biology, prior therapy and response to prior therapy and whether there is a need for chemo

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**LOCAL: Up to 5 years of therapy**

- Lumpectomy/Mastectomy +/− Radiation Therapy

**ADJUVANT: Up to 5 years of therapy**

- Al
- **Al + CDK4/6i**
- tam (SERM) +/− **Chemo***

Physician choice of one of the options above based on patient characteristics and tumor biology

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*Indications for Chemo include impending visceral crisis, endocrine resistance or other need for rapid debulking

Sources: American Cancer Society; UptoDate.com; Sammons et al. Target Oncol. (2019); industry knowledge

Tam: tamoxifen; Fulv: fulvestrant; DFS: Disease-Free Survival; mPFS: Median Progression-Free Survival; ORR: Objective Response Rate

(1) anastrozole, letrozole, exemestane; (2) abemaciclib, palbociclib, ribociclib; (3) copanlisib; (4) sirolimus, everolimus, temsirolimus
Segments of Therapy in ER+/HER2- Breast Cancer

First Pivotal Study will target 2L/3L therapy, followed by studies in 1L therapy setting

<table>
<thead>
<tr>
<th>LINE OF THERAPY</th>
<th>ER+ / HER2-¹</th>
<th>ER+ / HER2+²</th>
</tr>
</thead>
<tbody>
<tr>
<td>2L/3L+</td>
<td>~150K</td>
<td>~10K</td>
</tr>
<tr>
<td>1L</td>
<td>~115K</td>
<td>~285K+</td>
</tr>
<tr>
<td>High-Risk Adjuvant</td>
<td>~75K</td>
<td>~12 months</td>
</tr>
<tr>
<td>Early Breast Cancer</td>
<td>~285K+</td>
<td>~12 months</td>
</tr>
<tr>
<td>HER2+ w/ CNS Mets</td>
<td>~10K</td>
<td>~500M</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PATIENTS</th>
<th>DURATION OF THERAPY³</th>
<th>MARKET POTENTIAL⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>~150K</td>
<td>~2-12+ months</td>
<td>~$3-5B</td>
</tr>
<tr>
<td>~115K</td>
<td>~6-36+ months</td>
<td>$5-10B+</td>
</tr>
<tr>
<td>~75K</td>
<td>Up to 5 years</td>
<td>~$3-5B</td>
</tr>
<tr>
<td>~285K+</td>
<td>Up to 5 years</td>
<td>$10B+</td>
</tr>
<tr>
<td>~10K</td>
<td>~12 months</td>
<td>~$500M</td>
</tr>
</tbody>
</table>

¹2025 incidence projection estimates. Olema internal data, Informa ER+ HER2- BC Prevalence Based Market Forecast. 26% of adjuvant eligible patients assumed to have Ki-67 ≥ 20%. Early breast cancer incidence includes high risk adjuvant segment. ²2025 incidence projection estimates. Olema internal data, Informa HER2+ BC Prevalence Based Market Forecast. Forecast based on 2L+ ER+ HER2+ metastatic breast cancer projections. ³Olema internal data. ⁴2025 opportunity estimates for total endocrine therapy market (US and EUS). Olema internal data.
### Significantly Fewer Competing Programs for 2/3L and 1L MBC Treatment

#### 2L/3L ER+/HER2- MBC

<table>
<thead>
<tr>
<th>Year</th>
<th>Programs</th>
</tr>
</thead>
<tbody>
<tr>
<td>YE 2021</td>
<td>10 Active Programs</td>
</tr>
<tr>
<td>YE 2022</td>
<td>4 Active Programs</td>
</tr>
</tbody>
</table>

#### 1L ER+/HER2- MBC

<table>
<thead>
<tr>
<th>Year</th>
<th>Programs</th>
</tr>
</thead>
<tbody>
<tr>
<td>YE 2021</td>
<td>6 Active Programs</td>
</tr>
<tr>
<td>YE 2022</td>
<td>4 Active Programs</td>
</tr>
</tbody>
</table>
OP-1250: Best-in-Class Potential for ER+/HER2- Breast Cancer

Clinical dataset with over 160 patients treated with OP-1250 supports opportunity in both monotherapy and combination settings for patients with ER+/HER2- advanced metastatic breast cancer

**Complete ER Antagonism**
Dual activity as a next-generation CERAN / SERD to drive deeper, more durable responses in both wild-type and mutant ER

**Attractive PK Profile**
Highly favorable pharmacokinetics, oral bioavailability and 8-day half-life leading to steady-state plasma levels with minimal peak-to-trough variability

**Favorable Tolerability**
Favorable tolerability profile in heavily pretreated patients

**Robust Tumor Shrinkage**
Meaningful anti-tumor activity in both wild-type and mutant ER in preclinical models and durable benefit in clinical settings

**Combinability w/ CDK4/6i**
Combainable with Palbociclib – no DDI* and overall tolerability profile consistent with expected profile of palbociclib plus endocrine therapy

**CNS Penetration**
Demonstrated activity in nonclinical brain metastases studies

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Data referenced above as of October 26, 2022.
*In completed dose escalation cohorts from Phase 1b combination study with palbociclib. DDI = Drug Drug Interaction.
Phase 1/2 Monotherapy Clinical Update from ENA 2022
**OP-1250-001 First-in-Human Phase 1/2 Monotherapy Trial: Study Design**

**Phase 1a Dose Escalation**
- 30 mg
- 60 mg
- 120 mg
- 210 mg
- 300 mg

**Phase 1b Dose Expansion**
- 60 mg (n=25)
- 120 mg (n=25)
- RP2D of 120 mg

**Phase 2 Cohorts**
- Patients with measurable disease* (n=50)
- Patients with non-measurable disease* (n=15)
- Patients with CNS metastasis (n=15)

**Primary objectives**: Pharmacokinetics, safety and tolerability, identify RP2D

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

**Key Inclusion Criteria:**

**Phase 1a**
- Tumor must be ER+/HER2 negative
- At least one prior hormone-based therapy for locally advanced, recurrent, or metastatic disease
- 0-2 prior chemotherapy regimens for locally advanced or metastatic disease
- Measurable and non-measurable disease (evaluable disease)

**Phase 1b**
- Tumor must be ER+/HER2 negative
- 1-4 prior hormone-based therapy for locally advanced, recurrent, or metastatic disease
- 0-1 prior chemotherapy regimens for locally advanced or metastatic disease
- Measurable disease by RECIST 1.1 Criteria

*Fully-enrolled.

CBR: Includes patients who received at least one cycle of treatment and had at least 1 postbaseline tumor assessment were evaluable for a response, and enrolled ≥24 weeks prior to the data cut-off date. CR, Clinical Benefit Rate; CR, Confirmed Response; ORR, Objective Response Rate; PR, Partial Response; RP2D, Recommended Phase 2 Dose; SD, Stable Disease
**OP-1250 Phase 1/2 Dose Expansion**  
**Patients Received Extensive Prior Therapies**

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

*Sums may not total to 100% due to rounding.

*Source: EMERALD Phase 3 trial in CDK 4/6 inhibitor-experienced 2/3L patients, Journal of Clinical Oncology.

AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinase 4/6; ECOG, Eastern Cooperative Oncology Group.

- 69% of patients received 2 or more prior lines of therapy in the advanced setting; 82% visceral disease
- 96% received prior CDK 4/6i; 81% received prior AI; 65% received prior fulvestrant
- 59% had activating mutations in ESR1
- Up to 50% of patients expected to be endocrine resistant*
Dose-Proportional PK with Optimal Steady-State Plasma Concentrations

- High oral bioavailability and steady-state plasma levels with minimal peak-to-trough variability allowing complete inhibition of the ER for the full dosing interval
- Dosing at the RP2D of 120 mg yields drug exposures that exceed the predicted efficacious threshold based on pre-clinical models
- Mean terminal half-life ($T_{1/2}$) = 8 days, supporting once-daily dosing

Dashed black line=target efficacious exposure based on estradiol-supplemented preclinical models ($C_{min}=226$ ng/mL) (8 studies); dotted red line=fulvestrant $C_{max}=28$mg dosed at 500mg every 28 days QD, once daily.
60 mg and 120 mg Doses Well Tolerated in Phase 1/2 Monotherapy Dose Expansion

<table>
<thead>
<tr>
<th>TRAEs in ≥15% of Patients in Phase 1a/1b</th>
<th>60 mg (n=33)</th>
<th>120 mg (n=35)</th>
<th>Total (60 mg &amp; 120 mg, n=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>≥Grade 3</td>
</tr>
<tr>
<td>Any TRAE</td>
<td>9</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

**Grade 3/4 Neutropenia**

Four out of 68 patients had Grade 3/4 neutropenia, occurring ~4-6 weeks into therapy and have recovered
- 1 patient had Grade 3 neutropenia at 120 mg, discontinued due to concurrent disease progression; neutropenia recovered
- 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, discontinued, and recovered
  - 1 patient had febrile neutropenia with no evidence of infection, discontinued from treatment, and recovered
- Oncologists are comfortable monitoring for and managing neutropenia in breast cancer patients

**Other Grade 3 Events**

- Three additional grade 3 events assessed as potentially related to study drug:
  - Anemia (1 at 60 mg)
  - Nausea (1 at 120 mg)
  - Fatigue (1 at 120 mg)

TRAE, Treatment-Related Adverse Event
Data Cutoff Date: September 2, 2022
Meaningful Anti-Tumor Activity in OP-1250 Dose Expansion

41% of patients had a reduction in target lesion

Patient of Efficacy Population

ESR1\(^a\)  AI  CDK4/6  Chemotherapy  Fulvestrant

\(^a\)Patient had an unconfirmed partial response and later progressed at a subsequent scan.

\(^b\)Dark shaded boxes indicate ESR mutation present, light shaded 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.
Clear Efficacy and Durable Clinical Benefit in Heavily Pretreated Population

- Across all patients: 6 PRs out of 57 response-evaluable patients (4 cPRs and 2 uPRs*)
- In ESR1 mutant patients: 4 PRs out of 22 response-evaluable patients (3 cPRs and 1 uPR*)
- 39% CBR at RP2D of 120 mg (7/18)
- 32% CBR across both doses (11/34)
- Data maturing with 31% of patients remaining on treatment as of Sept 2, 2022

*Solid boxes indicate ESR mutation present, open boxes indicate wild-type, and the absence of a box indicates missing data.
*Unconfirmed partial responses awaiting confirmation at a subsequent scan.
AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; Chemo, chemotherapy; Fulv, fulvestrant; PD, progressive disease; PR, partial response.
Phase 1/2 Dose Expansion Summary

OP-1250 is a Phase 3-ready asset with an emerging best-in-class profile

A complete ER-antagonist with attractive PK, high drug exposures and a long-half life

<table>
<thead>
<tr>
<th>Heavily Pre-treated Patients</th>
<th>Best-in-Class Emerging Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>82%</strong> of patients had visceral disease at baseline</td>
<td><strong>84%</strong> of TRAEs were Grade 1 / 2 in severity with no MTD</td>
</tr>
<tr>
<td><strong>96%</strong> of patients were CDK 4/6 inhibitor experienced</td>
<td><strong>41%</strong> of target tumor lesions reduced in size</td>
</tr>
<tr>
<td><strong>65%</strong> of patients had prior fulvestrant</td>
<td><strong>4 + 2</strong> Confirmed / Unconfirmed partial responses*</td>
</tr>
<tr>
<td><strong>69%</strong> 2 or More Prior Lines in the Advance Setting</td>
<td><strong>39%</strong> CBR at RP2D of 120 mg; 31% of patients still on therapy; efficacy maturing</td>
</tr>
</tbody>
</table>

**Up to 50% of patients expected to be endocrine resistant**

**Clinically meaningful durable responses in endocrine sensitive patients**

*Unconfirmed partial responses awaiting confirmation at a subsequent scan.

**Source: EMERALD Phase 3 trial in CDK 4/6 inhibitor-experienced 2/3L patients, Journal of Clinical Oncology.
Data cut as of September 2, 2022.
Phase 1b Combination Study Update from SABCS 2022
Phase 1b Combination Study with Palbociclib: Study Design

Initiated January 2022

Key Inclusion Criteria:
- ER+/HER2- advanced breast cancer
- Evaluable disease (measurable and non-measurable)
- ≤ 1 prior hormonal regimen for locally advanced or metastatic disease
- Can be CDK4/6i naïve or pre-treated

Dose Escalation

OP-1250 120 mg + Palbociclib 125 mg
- 3+3 design
- N=12 patients

Dose Expansion

OP-1250 120 mg + Palbociclib 125 mg
- N=30 - 40 patients

Objectives: Safety, tolerability and antitumor activity of OP-1250 at RP2D in combination with palbociclib

Primary objectives: Pharmacokinetics, safety and tolerability, identify RP2D of OP-1250 for combination with palbociclib
Secondary objectives: ORR (CR + PR), CBR (CR + PR + SD ≥24 weeks)

CBR, clinical benefit rate; ORR, objective response rate; CR, complete response; PR, partial response; SD, stable disease; RP2D, recommended phase 2 dose
### Patient characteristics

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

\(^a\)Sums may not total to 100% due to rounding.

AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinase 4/6; ECOG, Eastern Cooperative Oncology Group.
OP-1250 Phase 1b Dose Escalation in Combination with Palbociclib
Well Tolerated with No DLTs

Safety

- No DLTs were observed during dose escalation and MTD was not reached
- No dose-related increase in the incidence or severity of adverse events was observed
- Majority of TEAEs were grade 1 or 2
  - Increasing dose did not show increase in frequency
  - Frequently reported TEAEs included neutropenia, nausea, vomiting, anemia, and gastroesophageal reflux disease
- 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
  - Rate of neutropenia consistent with the FDA-approved label for palbociclib plus an endocrine therapy (PALOMA 2
    - overall incidence of neutropenia was 80% with 56% grade 3 and 10% grade 4)
- No Grade 4 neutropenia was reported

<table>
<thead>
<tr>
<th>TEAEs in ≥15% of Patients</th>
<th>Total (N=12)</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia*</td>
<td></td>
<td>1</td>
<td>2</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Anemia</td>
<td></td>
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<tr>
<td>GERD</td>
<td></td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>COVID-19</td>
<td></td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td></td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sinus bradycardia</td>
<td></td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>UTI</td>
<td></td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>WBC count decreased</td>
<td></td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

* Includes adverse events reported as either “Neutropenia” or “Neutrophil count decreased.”

TEAE, Treatment-Emergent Adverse Event. UTI, urinary tract infection, WBC, white blood cell
Data Cutoff Date: September 12, 2022

† Ibrance (palbociclib) prescribing information. Pfizer Inc. 2019.
OP-1250 Phase 1b Dose Escalation in Combination with Palbociclib
No drug-drug interaction observed between OP-1250 and Palbociclib

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
- 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

Steady State $C_{\text{max}}$ of OP–1250 Combination vs. Single Agent

Steady State $AUC_{(0-24)}$ of OP–1250 Combination vs. Single Agent
OP-1250 Phase 1b Dose Escalation in Combination with Palbociclib

No drug-drug interaction observed between OP-1250 and Palbociclib

• No drug-drug interaction between palbociclib and OP-1250 in the dose range of 30 to 120 mg

• OP-1250 did not affect palbociclib 125 mg exposures when compared to published concentrations

• Exposure of palbociclib was within 90% of reported geometric means values for palbociclib

Steady State $\text{AUC}_{0-24}$ and $C_{\text{max}}$ of Palbociclib vs. Published Concentrations$^a$

$^a$Figure includes all doses of OP-1250. N=12 patients.
8 of 12 patients remain on treatment as of data cutoff Sept. 12, 2022

Data continues to mature with stable disease lasting ≥24 weeks and ongoing for 2 patients; longest duration of treatment in the study is 31 weeks

4 patients have discontinued treatment due to disease progression

Phase 2 dose expansion in up to 30 additional patients at 120mg OP-1250 in combination with palbociclib ongoing

---

Duration of Treatment as of September 15, 2022

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.
**Phase 1b Combination Study with Ribociclib and Alpelisib**

**Initiated Q3 2022**

**Dose Escalation**

- **1L+ ER+ MBC (CDK4/6 naïve or previously treated)**
  - OP-1250
    - 30 mg
    - 60 mg
    - 120 mg

- **Patients with PIK3CA mutation**
  - OP-1250
    - 30 mg
    - 60 mg
    - 120 mg

**Dose Expansion**

- **Ribociclib**
  - 600 mg
- **Alpelisib**
  - 300 mg

- **RP2D OP-1250**
  - + Ribociclib 600 mg
  - + Alpelisib 300 mg

**Objectives:**

- **Signaling Activity**

**Primary objectives:** Pharmacokinetics, safety and tolerability, identify RP2D of OP-1250 for combination with either ribociclib or alpelisib

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

**Initiated Q3 2022**

• N=30 patients

• 3+3 design

**Objectives:** Safety, tolerability and antitumor activity of OP-1250 at RP2D in combination with either ribociclib or alpelisib
Rapidly Advancing Toward Phase 3
## Rapidly Advancing OP-1250 Toward Pivotal Phase 3 Studies

| Monotherapy | Phase 1a Dose Escalation | Dose Range of 30 mg to 300 mg  
Completed n=42 |
|--------------|--------------------------|--------------------------------|
| Phase 1b Dose Expansion | Dose Expansion at 60 mg and 120 mg  
Completed Enrollment n=56 |
| Phase 2 | Measurable Disease  
Completed Enrollment n=50 |
| Non-measurable Disease  
Completed Enrollment n=15 |
| CNS Mets  
Enrollment ongoing |
| 2L/3L Pivotal Phase 3 | | ![Initiation planned for mid-2023; End-of-Phase 2 meeting with FDA in Q1 2023](image) |

### Combination Therapy

| OP-1250 w/ Palbociclib | Successful Dose Escalation through 120 mg  
P2 Dose Expansion at 120 mg ongoing |
| OP-1250 w/ Ribociclib or Alpelisib | P1b Dose Escalation ongoing |
| 1L Pivotal Phase 3 w/ Ribociclib or Palbociclib | ![Pivotal Phase 3 planned for 2024](image) |
Delivering on Value Creating Milestones

H1: 2023
Phase 2 monotherapy data

Mid-2023
Initiate pivotal Phase 3 2/3 L monotherapy study

H2: 2023
CDK 4/6i combination therapy data

2024
Initiate pivotal Phase 3 combination study with CDK 4/6i

Strong cash position of $222.6M\(^{(1)}\) to support clinical development and operations into 2H 2024

\(^{(1)}\) As of September 30, 2022.
Leading the Next Generation of Oral CERAN/SERDs for the Treatment of ER+/HER- Metastatic Breast Cancer (MBC)

**OP-1250, Best-in-Class CERAN/SERD for ER+/HER2- MBC**
- Completely shuts down estrogen receptor signaling pathways in women with ER+/HER- MBC
- Internally-discovered, wholly-owned IP with no royalty burden

**Clinical Validation as a Monotherapy and in Combo w/ CDK4/6i**
- Over 160 patients treated to date with OP-1250
- Highly encouraging Phase 1/2 clinical results in both monotherapy and combination studies

**Initiating 1st Pivotal Phase 3 monotherapy study in mid-2023**
- FDA Fast Track designation in 2L+ ER+/HER2- MBC
- Combination studies ongoing with Ibrance®, Kisqali® and Piqray®

**Multi-Billion Dollar Commercial Market Opportunity**
- 2L/3L+ MBC, represents a $3-5B commercial opportunity
- 1L MBC in combination with CDK 4/6i, represents a $5-10B commercial opportunity

Strong cash position of $222.6M(1) to support clinical development and operations into 2H 2024

(1) As of September 30, 2022.
Understanding OP-1250’s Mechanism of Action
OP-1250: a Complete Estrogen Receptor ANtagonist (CERAN)

OP-1250 potently and completely inactivates the Estrogen Receptor (ER), blocks ER-driven transcriptional activity, inhibits ER-driven breast cancer cell growth, and strongly induces degradation of ER.

Partial Antagonists Have a Short Duration of Response for Treatment of Metastatic Breast Cancer

Complete antagonists turn off AF2 and recruit N-CoR to inactivate AF1

AF1: activation factor 1
AF2: activation factor 2

Both CERAN/SERDs and SERM/SERDs Are Strong Degraders of ERα

OP-1250 and CERAN/SERDs strongly degraded the estrogen receptor (ER) in five ER+ cell lines

Partial and strong agonists demonstrated variable and inconsistent ER degradation

Estradiol (E2), the prototypical agonist of ERα, degraded ERα in all five ER+ cell lines

In all cases, none of the compounds achieved full ER degradation; complete ER antagonism is independent from degradation and key to inactivating remaining ER receptor

CERAN/SERDs Inactivate Both AF1 & AF2 Activity, While SERM/SERDs Only Inactivate AF2

CERAN/SERDs completely inactivate AF1 activity of the estrogen receptor, while partial and strong agonists (SERM/SERDs) do not fully inhibit AF1 activity.

Xenograft Efficacy Studies: OP-1250 vs. Fulvestrant
OP-1250 Demonstrates Tumor Shrinkage Across Multiple Xenograft Models

**MCF-7 (HER2/neu)**

**HCC1500**

**ST941**

**HCI-013**

- Vehicle
- OP-1250 10 mg/kg
- OP-1250 100 mg/kg
- Vehicle
- OP-1250 30 mg/kg/day
- Fulvestrant 5 mg/mouse/week
- OP-1250 10 mg/kg/day
- OP-1250 10 mg/kg/day
- Vehicle
- OP-1250 1 mg/kg
- OP-1250 3 mg/kg
- Fulvestrant 5 mg/kg
- OP-1250 6.1 mg/kg
- OP-1250 10 mg/kg
- OP-1250 0.3 mg/kg
- OP-1250 1 mg/kg + Palbo 75 mg/kg
- Vehicle (0.5% CMC)
- OP-1250 0.3 mg/kg
- OP-1250 3 mg/kg
- Fulvestrant 10/25 mg/kg
- OP-1250 10 mg/kg
- OP-1250 0.3 mg/kg
- OP-1250 3 mg/kg
- Palbo 75 mg/kg
- OP-1250 1 mg/kg

*Images show tumor volume changes over time for each model with different treatments.*
OP-1250 Has Demonstrated Activity in CNS Metastases Models

AACR 2021: Intracranial Breast Cancer Brain Metastases Xenograft Study

10 mg/kg OP-1250 is superior to tamoxifen, fulvestrant and ovariectomy in shrinking mutant ESR1-Y537S tumors in an intracranial model of ER+ breast cancer brain metastasis

After 100 days, tumors in mice treated with OP-1250 remain small or undetectable while tumors in mice treated with fulvestrant and tamoxifen have started to grow.

Reference: Hodges-Gallagher et al., Proceedings: AACR Annual Meeting 2021; April 9-14, 2021