# OP-1250: Phase 1 Clinical Update

November 30, 2021

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# Introduction

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# OP-1250: Best-in-Class Potential for ER+ / HER2- Breast Cancer


### Highly Attractive Pharmacokinetic Profile

- Orally-bioavailable with long half-life, providing PK profile with low intra-day variability
- Enables complete antagonism of the estrogen receptor without the need for higher daily doses

### Favorable Tolerability Profile in Heavily Pretreated Patient Population

- Phase 1 patient enrollment with significant prior CDK4/6i, chemotherapy and fulvestrant treatment
- Generally well-tolerated with no dose-limiting toxicities and maximum tolerated dose not reached

### Robust Anti-Tumor Activity Demonstrated with Long Duration of Patient Benefit

- 3 partial responses in patients with ESR1 mutations (2 confirmed, 1 unconfirmed)
- Overall Response Rate of 17% (2/12) and Clinical Benefit Rate of 46% (6/13) in targeted RP2D range
- Robust target lesion reduction and duration of therapy extending beyond 1 year

### Rapidly Advancing Clinical Development Program

- Phase 1a successfully completed; Efficacy data continuing to mature
- Dose expansion ongoing with Phase 2 cohorts and first CDK4/6i combination study to initiate in Q1 2022
- Expect to enroll 100+ additional patients across development program in 2022

CDK4/6i: cyclin-dependent kinases inhibitor

# OP-1250: Designed to Address Unmet Need in Patients with Advanced ER+/HER2- Breast Cancer

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# ER+ Breast Cancer — A Significant Unmet Need

APPROXIMATELY

**282K WOMEN**

**in the U.S. will be diagnosed with breast cancer in 2021**

OVER

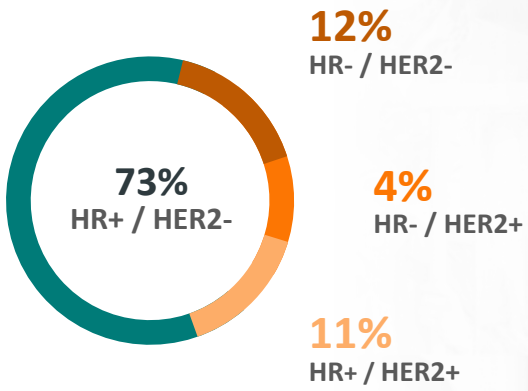
**43,600 WOMEN**

**in the U.S. will die from metastatic breast cancer in 2021**

## It's Estimated That Breast Cancer Accounts for 30% of New Cancer Diagnoses in U.S. Women

### Majority of All Breast Cancers

express Estrogen Receptor (ER+)



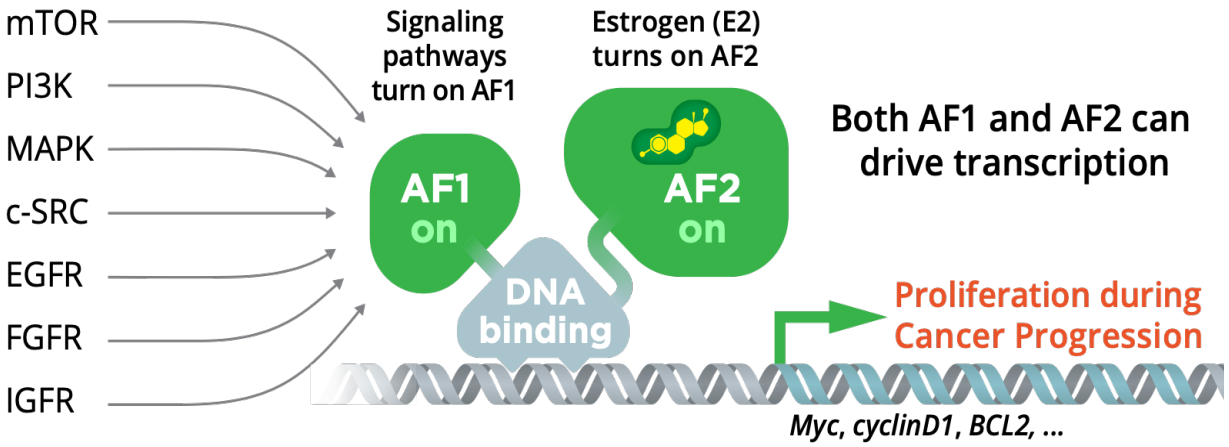

### Approximate $10B Market

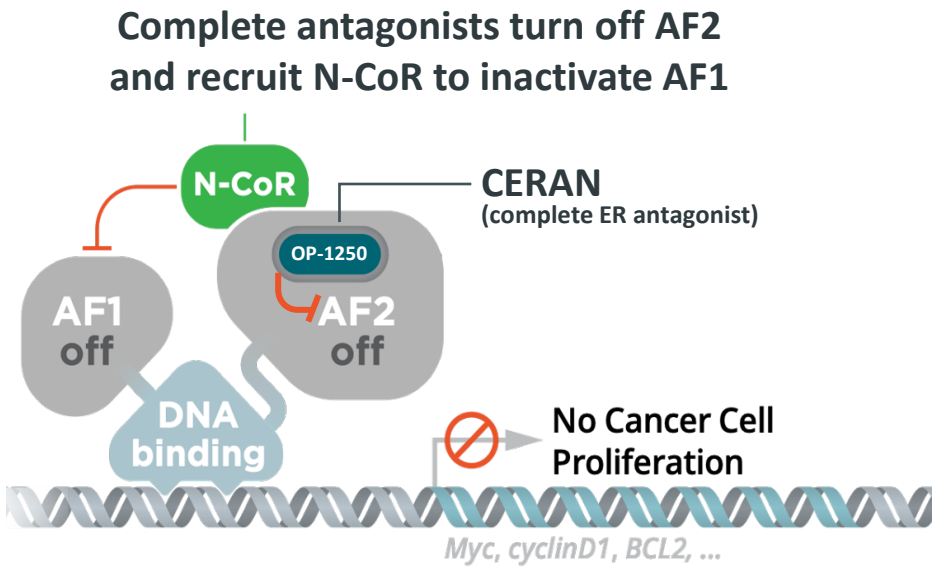
for endocrine therapies and targeted agents for ER+ breast cancer


References: American Cancer Society. Facts and Figures 2021; SEER database

# 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




AF1: activation factor 1
AF2: activation factor 2

References: Shang and Brown, *Science*, 2002: Vol. 295, Issue 5564, pp. 2465-2468 ; Webb, Nguyen, and Kushner, *JBC*, 2003: Vol. 278, pp. 6912–6920

# OP-1250: Non-Clinical Data Summary

**Complete Antagonism of ER:**

Activity in both wild-type and mutant ESR1 models by turning-off both AF1 and AF2 transcriptional activation domains

**Robust Tumor Shrinkage:**

Superiority vs. fulvestrant in head-to-head nonclinical studies

**Combination Therapy:**

Demonstrated additive effects in nonclinical models with other targeted agents

**Strong Degradation of ERα:**

Across all tested ER+ cell lines

**CNS Penetration:**

Robust activity in nonclinical brain metastases studies

**Attractive PK Profile:**

Orally bioavailable and attractive steady-state plasma levels

**OP-1250 has the potential to become best-in-class endocrine therapy of choice for ER+ breast cancer**

# OP-1250: Interim Phase 1 Clinical Data

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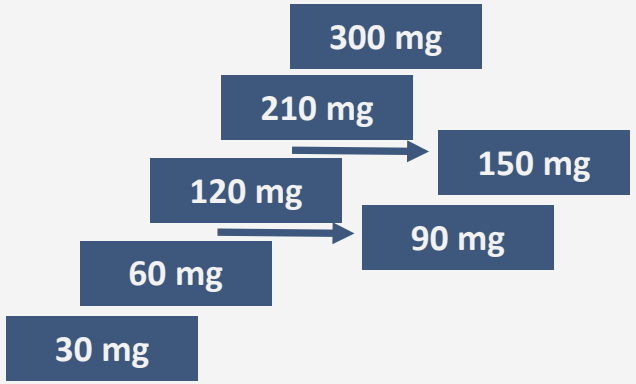
# First-in-Human Phase 1/2 Clinical Study Design

## OP-1250 oral, once-daily dosing

### Phase 1a Dose Escalation



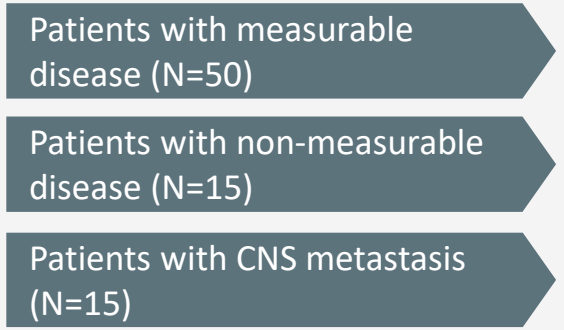

- Measurable and non-measurable disease

### Phase 1b Dose Expansion


- Measurable disease only

Primary objectives: Pharmacokinetics, safety and tolerability, identify RP2D
Secondary objectives: ORR (CR + PR); CBR (CR + PR + SD ≥24 weeks)

### Phase 2 Cohorts




Objectives: Antitumor activity in measurable disease cohort; safety and tolerability at RP2D

**Phase 1a Key Inclusion Criteria:**

- ER+/HER2- advanced breast cancer
- ≥1 prior endocrine therapy for advanced breast cancer
- ≤2 prior chemotherapy regimens for locally advanced or metastatic disease

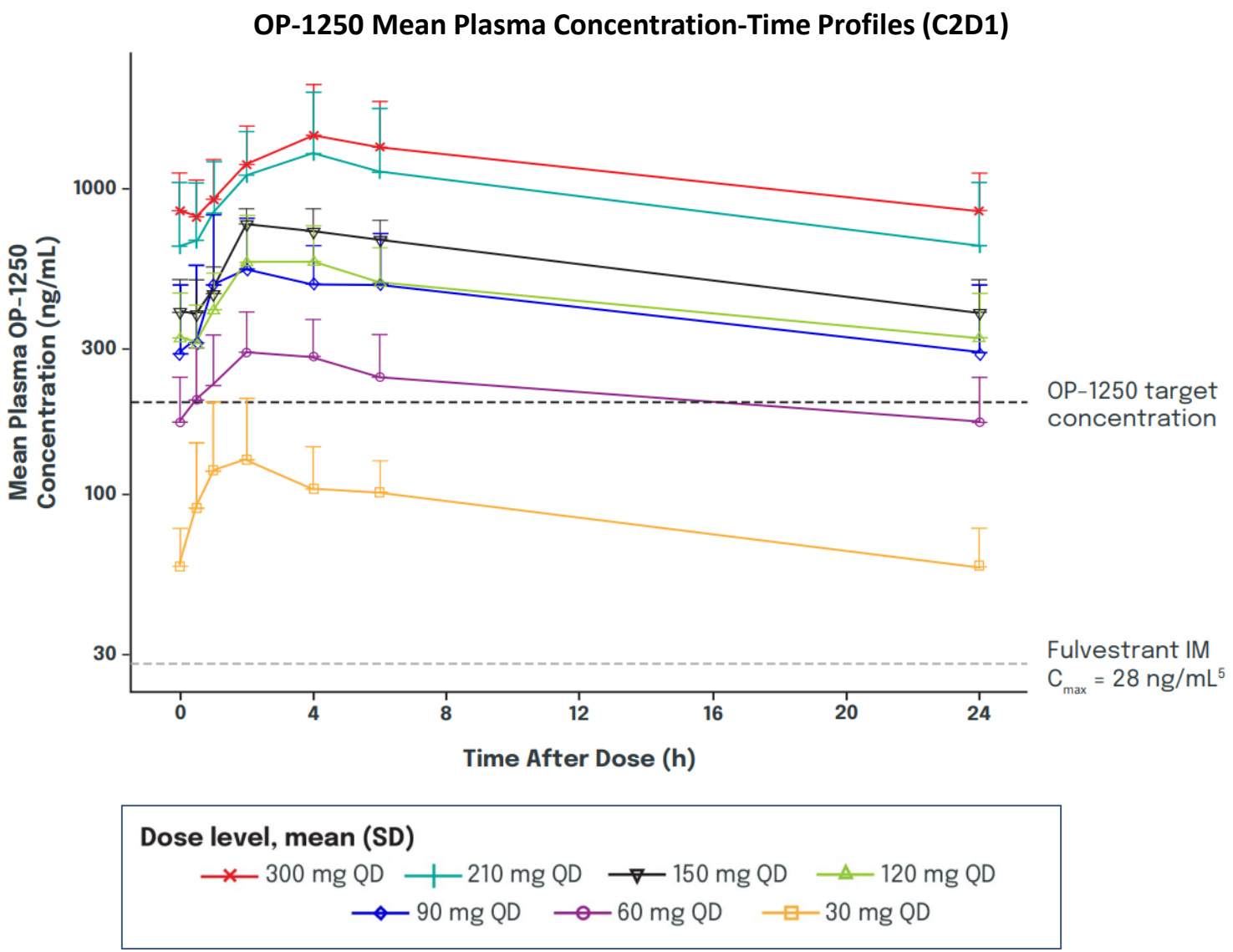
CNS, central nervous system; CBR, clinical benefit rate; ORR, overall response rate; CR, complete response; PR, partial response; SD, stable disease; RP2D, recommended phase 2 dose

# OP-1250 Phase 1 Study Population Received Extensive Prior Therapy

| Patient Characteristics | N=41 (%*) |
|---|---|
| **Median age (years)** | 63 |
| **ECOG performance status** | |
| 0 | 17 (41) |
| 1 | 24 (59) |
| **Measurable disease at baseline** | 31 (76) |
| **Visceral disease (liver, lung, peritoneum, pleura, ascites)** | 25 (61) |
| **Prior lines of therapy in advanced settings** | Median=3<br>(Range 1-8) |
| **Prior lines of endocrine therapy in advanced settings**† | Median=2 |
| 1 | 12 (29) |
| 2 | 13 (32) |
| 3 or more | 15 (37) |
| **Types of prior therapies in advanced settings** | |
| Chemotherapy | 17 (42) |
| Aromatase inhibitor (AI) | 31 (76) |
| Fulvestrant | 28 (68) |
| CDK 4/6 inhibitor | 39 (95)‡ |
| ***ESR1* mutations at baseline (ctDNA)**, n=39 evaluated | 19 (49)§ |

*Sums may not total to 100% due to rounding †One patient had missing data ‡Nine patients received 2 prior CDK4/6i regimens
§ctDNA was not collected in 2 patients. ECOG, Eastern Cooperative Oncology Group; CDK4/6, cyclin-dependent kinases

# Dose-Proportional PK with Attractive Steady-State Plasma Concentrations




- High oral bioavailability and steady-state plasma levels with minimal peak-to-trough variability
- Doses ≥60 mg QD exceed predicted efficacy thresholds
- Enables complete antagonism of the estrogen receptor without the need for higher daily doses
- Effective half life ($T_{1/2}$)=51-73 hours, supporting once-daily dosing

# Favorable Tolerability Profile

| TRAEs in ≥15% of Patients | 30 mg (n=5) | | 60 mg (n=6) | | 90 mg (n=6) | | 120 mg (n=6) | | 150 mg (n=4) | | 210 mg (n=7) | | 300 mg (n=7) | | Total N=41 (%) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | All | G≥3 | All | G≥3 | All | G≥3 | All | G≥3 | All | G≥3 | All | G≥3 | All | G≥3 | All | G≥3 |
| Patients with ≥1 event | 4 | 1 | 3 | 0 | 2 | 0 | 5 | 0 | 2 | 1 | 6 | 1 | 6 | 1 | 28 (68) | 4 (10)* |
| Nausea | 1 | 0 | 2 | 0 | 1 | 0 | 5 | 0 | 1 | 0 | 4 | 0 | 6 | 1 | 20 (49) | 1 (2) |
| Fatigue | 2 | 0 | 3 | 0 | 0 | 0 | 1 | 0 | 1 | 1 | 3 | 0 | 4 | 0 | 14 (34) | 1 (2) |
| Vomiting | 0 | 0 | 1 | 0 | 1 | 0 | 2 | 0 | 0 | 0 | 1 | 0 | 4 | 0 | 9 (22) | 0 |
| Headache | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 4 | 0 | 7 (17) | 0 |

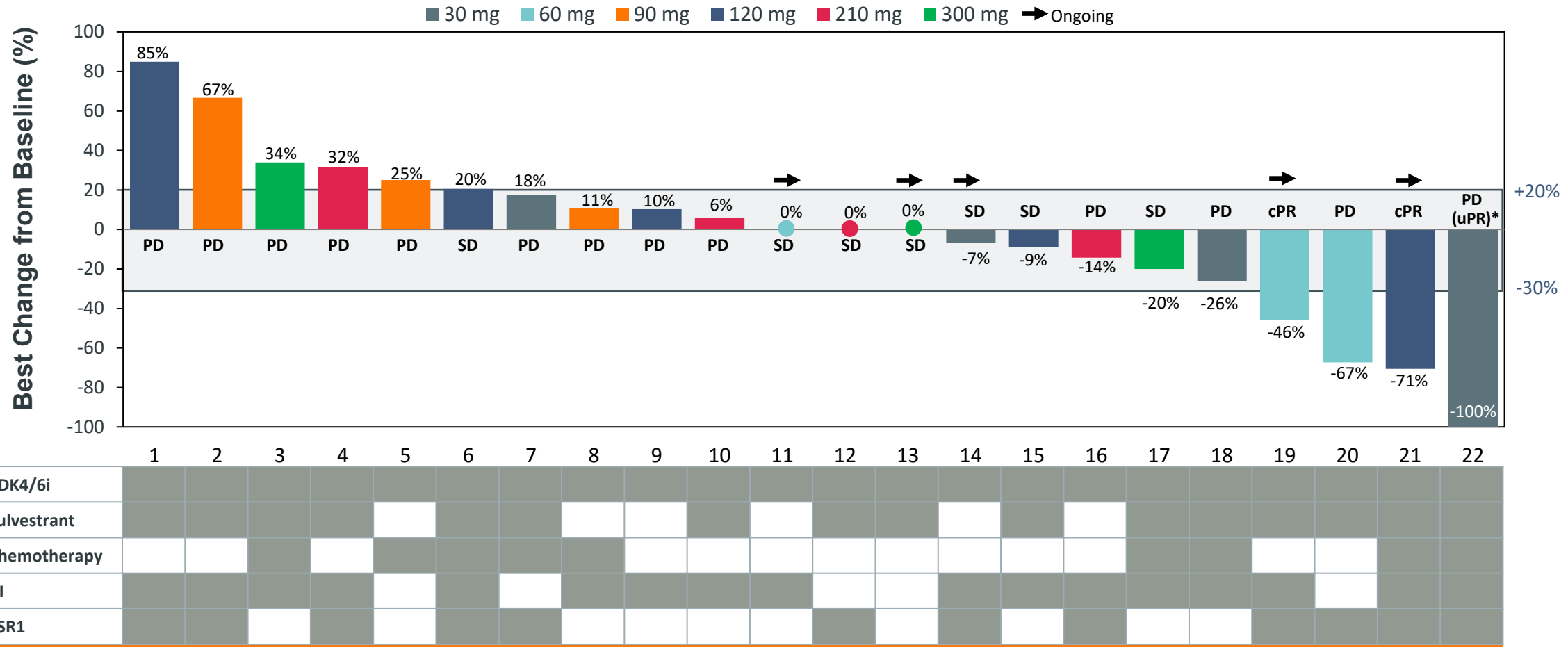
- Adverse events primarily grade 1 or 2 across all dose levels
- No dose limiting toxicities and maximum tolerated dose not reached
- No clinically significant bradycardia, ocular toxicity or diarrhea

**Targeted RP2D range of 60 to 120 mg based on pharmacokinetics, favorable tolerability, and initial efficacy**

*As of data cut-off of November 1, 2021, 3 patients had grade 4 neutropenia attributed to study drug by the investigator that did not reach ≥15%. Two of these patients presented with fever and neutropenia. TRAE, treatment-related adverse event as assessed by study investigator.

# OP-1250 Demonstrated Meaningful Anti-Tumor Activity

## Best Response of Target Lesion in Patients with Measurable Disease (N=22)




**Robust target lesion reduction up to 100% observed in response-eligible patients**

*Patient's response unconfirmed due to progression with a new non-target lesion at follow-up visit.
Efficacy-evaluable patients include those with measurable disease at baseline and at least one post-baseline scan. Data cut-off: November 1, 2021.
CDK4/6i, cyclin-dependent kinases inhibitor; AI, aromatase inhibitor.

# Case Study 1: Confirmed Partial Response in Late-Line Patient with Peritoneal Carcinomatosis and Bone Metastasis; Lymph Node Lesion Normalized and Resolution of Peritoneal Stranding and Ascites

**41-year-old female**
**120 mg OP-1250 QD**
**Confirmed Partial Response Maintained ≥9 months**

## Prior Therapy in Advanced / Metastatic Setting

**CDK4/6i:**

- Palbociclib

**Endocrine Therapies:**

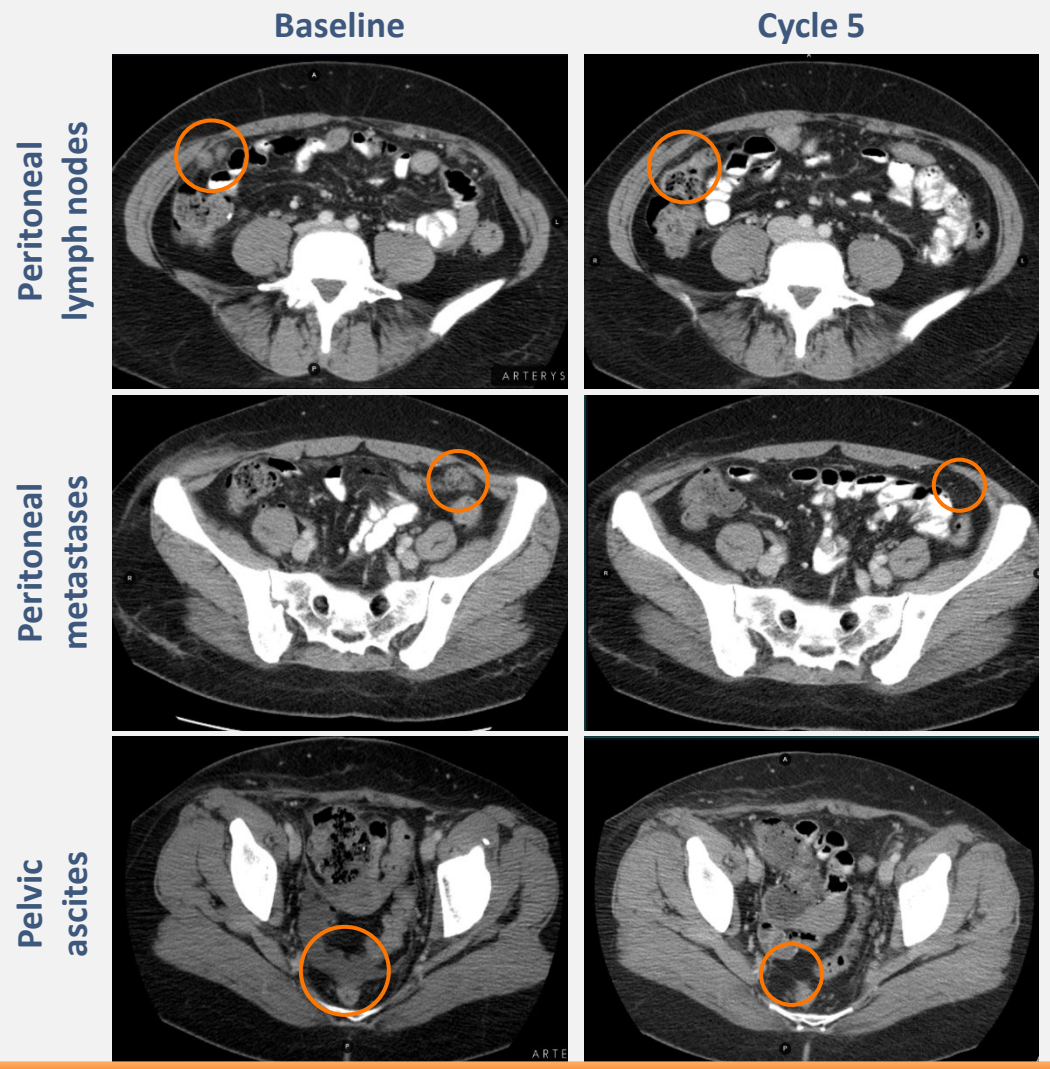
- Aromatase inhibitors: Anastrozole
- Leuprolide
- Tamoxifen
- Fulvestrant

**Chemotherapy:**

- ACT
- Capecitabine

## ESR1 Mutation

**Y537S**




**71% reduction in target lesions**

Responses evaluated per RECIST version 1.1. CDK4/6, cyclin-dependent kinases.

# Case Study 2: Confirmed Partial Response in Late-Line Patient with Multiple Liver Metastasis

**61-year-old female**
**60 mg OP-1250 QD**
**Confirmed Partial Response Maintained ≥8 months**

## Prior Therapy in Advanced / Metastatic Setting

**CDK4/6i:**

- Ribociclib

**Endocrine Therapies:**

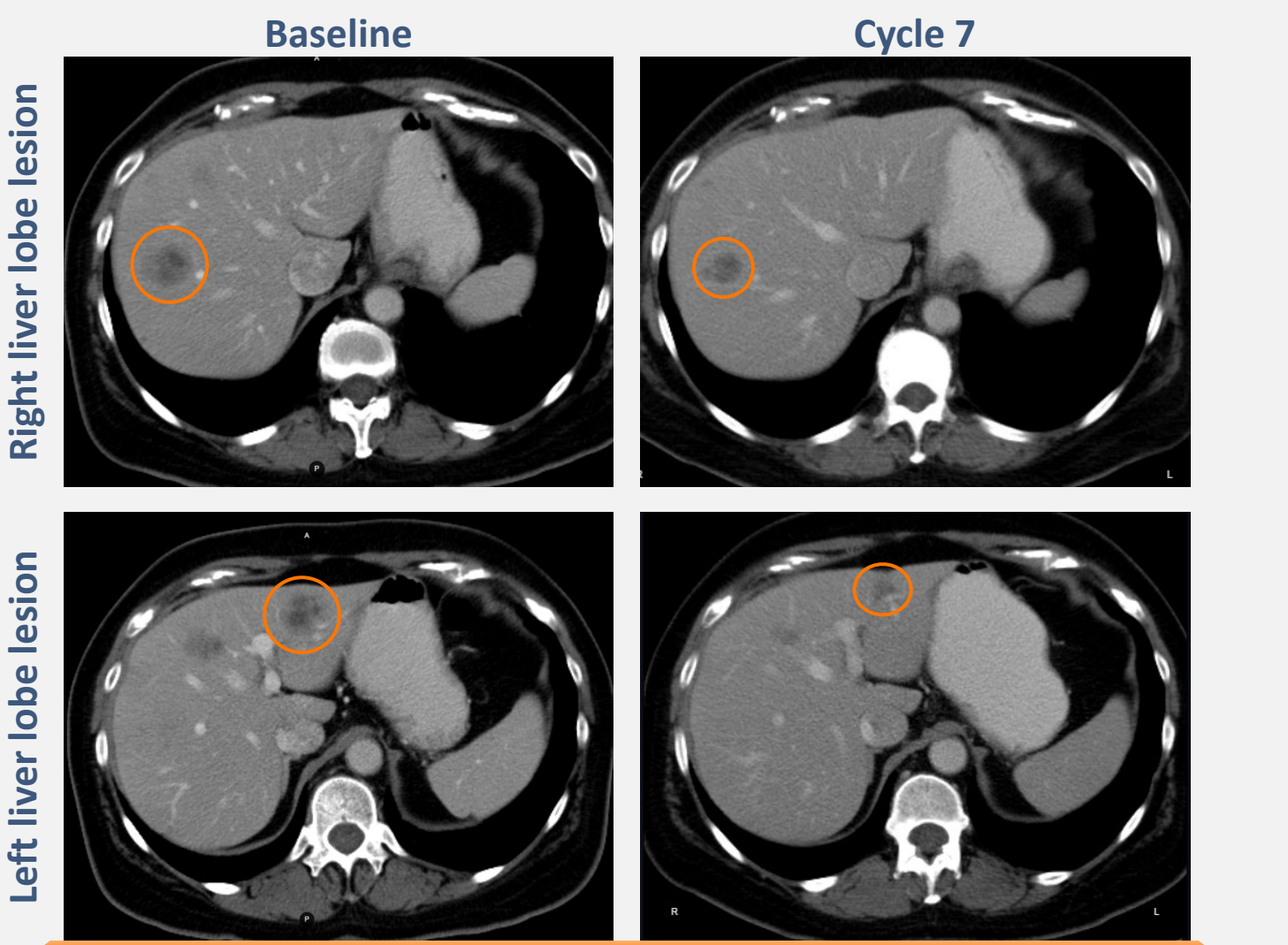
- Aromatase Inhibitors:
  Letrozole, Anastrozole, Exemestane
- Tamoxifen
- Fulvestrant

**Other Targeted Agents:**

- mTOR inhibitors: Everolimus

## ESR1 Mutation

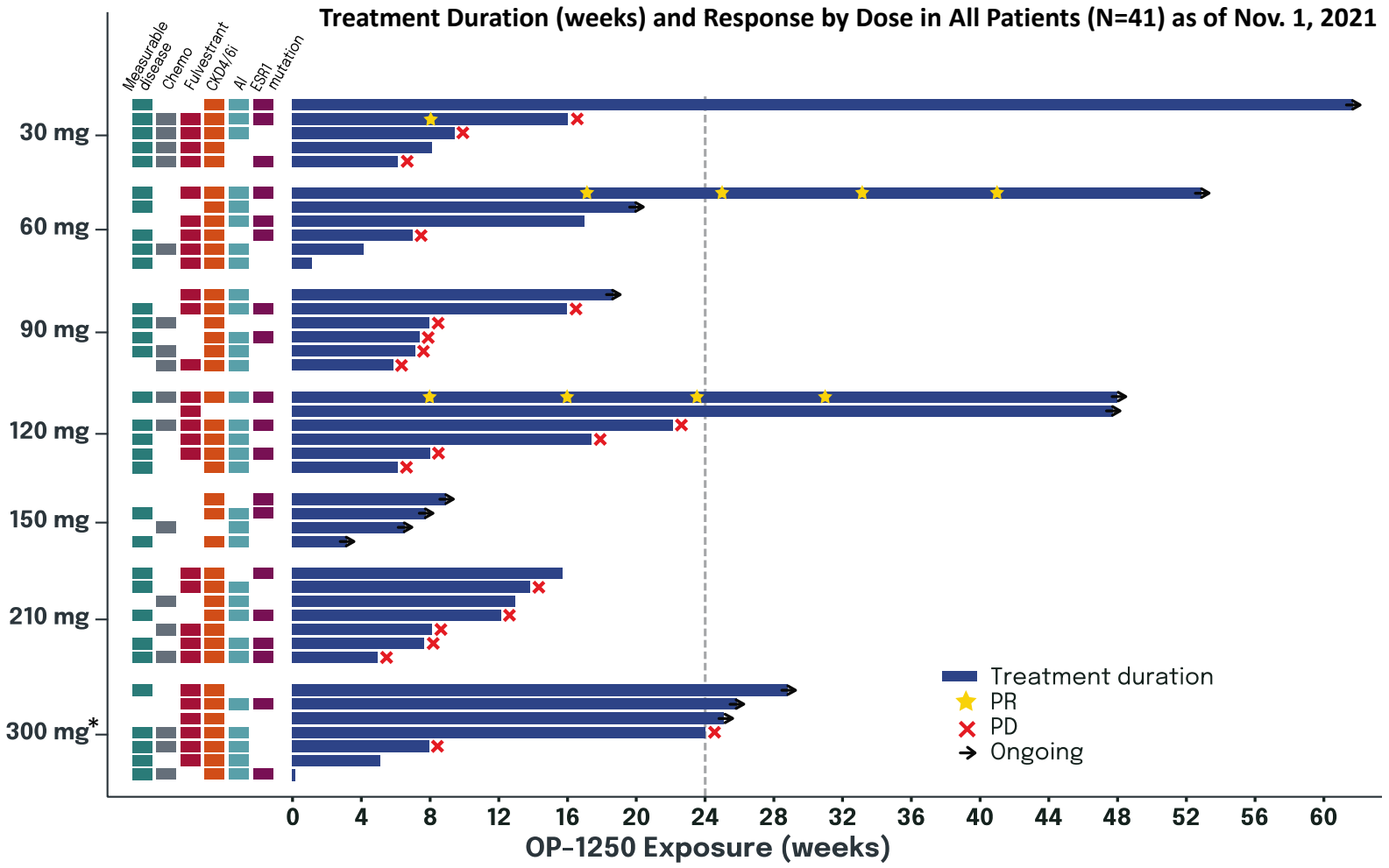
**Y537S**




**46% reduction in target lesions**

Responses evaluated per RECIST version 1.1. CDK4/6, cyclin-dependent kinases; mTOR, mechanistic target of rapamycin.

# Durable Clinical Benefit Observed in Heavily Pretreated Population




- Across dose levels:
  ORR: 8% (2/24) , CBR: 29% (7/24)
- RP2D range (60-120 mg):
  ORR: 17% (2/12), CBR: 46% (6/13)

- 2 confirmed partial responses (cPR) maintained ≥8 months; both patients remain on treatment

- 1 patient had 100% target lesion reduction on 30 mg OP-1250; response remained unconfirmed due to PD with new lesion identification at a follow-up visit

- Long duration of benefit, with 8 patients on therapy ≥6 months and 2 ≥1 year

- 32% of patients (13/41) still on treatment, with data maturing

*Four patients in the 300 mg cohort dose reduced, 3 to 120 mg and 1 to 60 mg with most occurring at the beginning of cycle 2. These patients were included in RP2D CBR calculation. CBR defined as SD persisting ≥24 weeks, or a best response of confirmed CR or PR. ORR includes patients with measurable disease only. AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinases inhibitor.

# Thank You to Our Patients and Clinical Investigators!

***On Behalf of the Entire Olema Team***

# Perspectives and Next Steps

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# Promising Early Profile with Heavily Pretreated Patients vs. Phase 1 SERDs

| Drug Candidate | Phase 1 Study Start | Median Prior Lines of Therapy in Advanced Setting | Percent of Patients with Prior CDK4/6i | Percent of Patients with Prior Fulvestrant | Percent of Patients with Prior Chemotherapy | Overall Response Rate |
|---|---|---|---|---|---|---|
| **OP-1250 Overall** | **2020** | **3** | **95%** | **68%** | **42%** | **8%** |
| **OP-1250 RP2D Range** | | | **94%** | **67%** | **56%** | **17%** |
| ARV-471 | 2019 | 5 | 100% | 71% | 38% | 7% |
| LY3484356 | 2019 | 2 | 83% | 60% | 26% | 6% |
| rintodestrant | 2018 | 3 | 77% | 85% | 50% | 5% |
| ZN-c5 | 2018 | 2 | 68% | 46% | NR | 5% |
| camizestrant | 2018 | 3 | 62% | 53% | NR | 10% |
| amcenestrant | 2017 | 2 | 63% | 47% | 42% | 7% |
| giredestrant | 2017 | 1 | 59% | 38% | NR | 11% |

NR, not reported

Sources: Arvinas, Dec 2020 company presentation; LY3484356, ASCO 2021 poster; rintodestrant, ESMO 2019; ZN-c5, June 2021 company presentation; camizestrant, ASCO 2020 & SABCS 2020 posters; amcenestrant, ASCO 2020 poster; giredestrant, SABCS 2019 poster.

# OP-1250: Successful Phase 1 with Key Objectives Achieved

## Highly Attractive Pharmacokinetics

- High oral bioavailability
- Dose proportional PK with exposures supporting once-daily dosing
  - Smooth profile with minimal peak-to-trough variability
- Effective half-life of 51-73 hours
- Doses ≥60 mg QD exceed predicted efficacy thresholds
  - Enables complete antagonism of ER without the need for higher daily doses

## Favorable Tolerability

- Generally well tolerated
- Adverse events were mostly Grade 1 or 2 at all dose levels
- No DLTs observed and MTD not reached
- No clinically significant bradycardia, ocular toxicity, or diarrhea
- RP2D range of 60 to 120 mg identified based on favorable pharmacokinetics, tolerability, and initial efficacy

## Promising Anti-Tumor Efficacy

- Clear efficacy signals observed in heavily pretreated patients
- 3 partial responses observed in patients with ESR1 mutations*
  - 2 confirmed and 1 unconfirmed
  - Durable cPRs ≥8months
- RP2D range (60-120 mg):
  ORR: 17% (2/12), CBR: 46% (6/13)
- Robust target lesion reductions ≥30% observed in 4 response-eligible patients
- 13 of 41 (32%) patients remain on study; Efficacy data continues to mature

**Potential best-in-class backbone endocrine therapy of choice for ER+ breast cancer**

*Best overall response as of data cutoff date of November 1, 2021

# Rapidly Advancing Development Program to Support Broad Profile for OP-1250

## Anticipated milestones

### Q4 2021

- ✓ Complete Phase 1a dose escalation
- ✓ Initiate Phase 1b dose expansion at 60 mg and 120 mg dose levels (N=15 each)

### Q1 2022

- Select RP2D
- Initiate Phase 2 cohorts
  - Measurable disease (N=50)
  - Non-measurable disease (N=15)
  - CNS metastasis (N=15)
- Initiate 1st Phase 1b CDK4/6i combination study

### 2H 2022

- Initiate additional Phase 1b studies in combination with CDK4/6 and PI3Kα inhibitors
- Initiate Phase 1b HER2+ study

### 2023

- Initiate pivotal study

**2022: Present updated monotherapy and combination data**

**Continuing to build evidence supporting OP-1250 as a differentiated, best-in-class CERAN**

# Q&A

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