A Phase 1b Dose Escalation and Expansion Study of OP-1250 in Combination with Ribociclib or Alpelisib in Patients with Advanced and/or Metastatic Estrogen Receptor-Positive (ER+)/HER2– Breast Cancer

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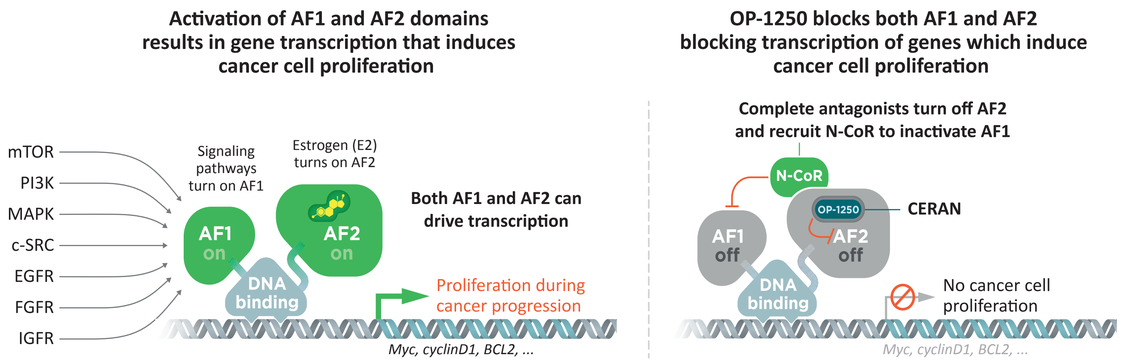
Background

- Addition of cyclin-dependent kinase (CDK) 4/6 inhibitors to endocrine therapies has improved progression-free survival and overall survival in patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2–) metastatic breast cancer (MBC), and is the first-line standard of care[1]
- Most estrogen receptor (ER)+ cancers that respond to therapy eventually develop resistance, highlighting an unmet need for more effective endocrine therapies[2]
- Addition of alpelisib, a PI3K inhibitor, to endocrine therapy significantly improved progression-free survival in patients with MBC,[3] and alpelisib plus fulvestrant is the current standard of care for second- or later-line treatment of *PI3KCA*-mutated HR+/HER2– MBC[1]
- OP-1250 is a small molecule oral complete estrogen receptor antagonist (CERAN) and selective estrogen receptor degrader (SERD) that blocks both transcriptional activation domains of the ER, thereby providing complete blockade of ER-driven transcriptional activity (**Figure 1**)[4]
- OP-1250 potently inactivates both the wild-type and mutant forms of ER, the latter of which confers ligand-independent activity as a mechanism of resistance to standard endocrine therapies[2]
- In an ongoing phase 1b combination trial of OP-1250 + palbocicilb, to date no drug-drug interaction and no induced metabolism of palbociclib dosed in combination with OP-1250 has been observed[5]

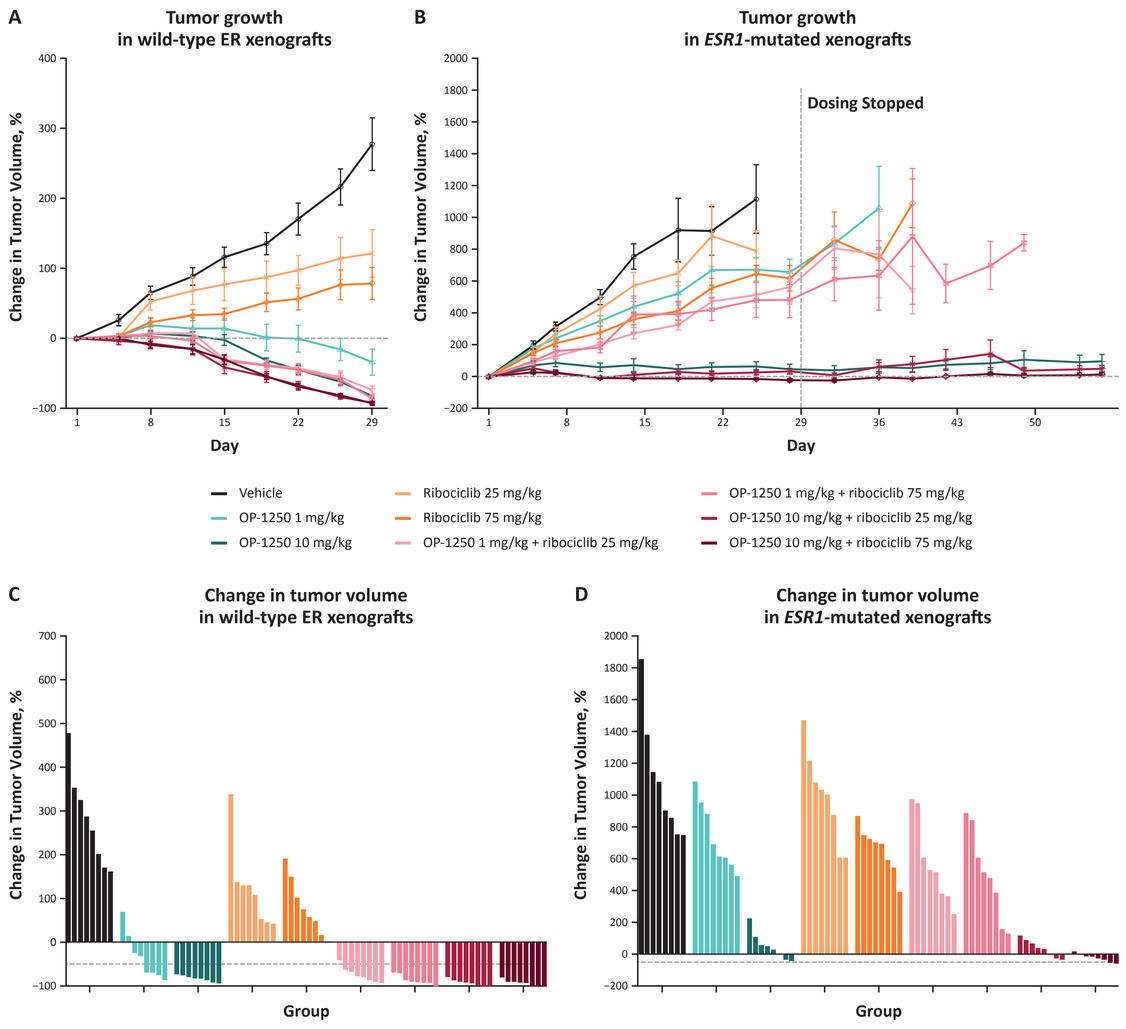
Figure 1. Mechanism of action of OP-1250 at the estrogen receptor[6,7]



AF, activation function; **CERAN**, complete estrogen receptor antagonist; **N-CoR**, nuclear receptor corepressor.

- In preclinical studies, the addition of CDK4/6 inhibitors markedly enhanced the tumor growth inhibition and tumor shrinkage observed with OP-1250 monotherapy in both wild-type ER and *ESR1*-mutated xenograft models (**Figure 2**)[8]
- OP-1250 is orally bioavailable with a favorable pharmacokinetic profile supportive of once-daily dosing; based on preclinical and clinical data, OP-1250 is not expected to change the PK of ribociclib and ribociclib is not expected to change the PK of OP-1250[5]

Figure 2. Combination OP-1250 and ribociclib treatment results in tumor growth inhibition (A, B) and tumor shrinkage (C, D) in xenograft breast cancer models with wild-type ER[a] and those with *ESR1*-activating mutations[b,8])



Note: Dotted lines represent tumor stasis. [a]MCF-7 xenograft model. [b]*ESR1*^{Y537S} tumor model ST941. **ER**, estrogen receptor.

Objectives

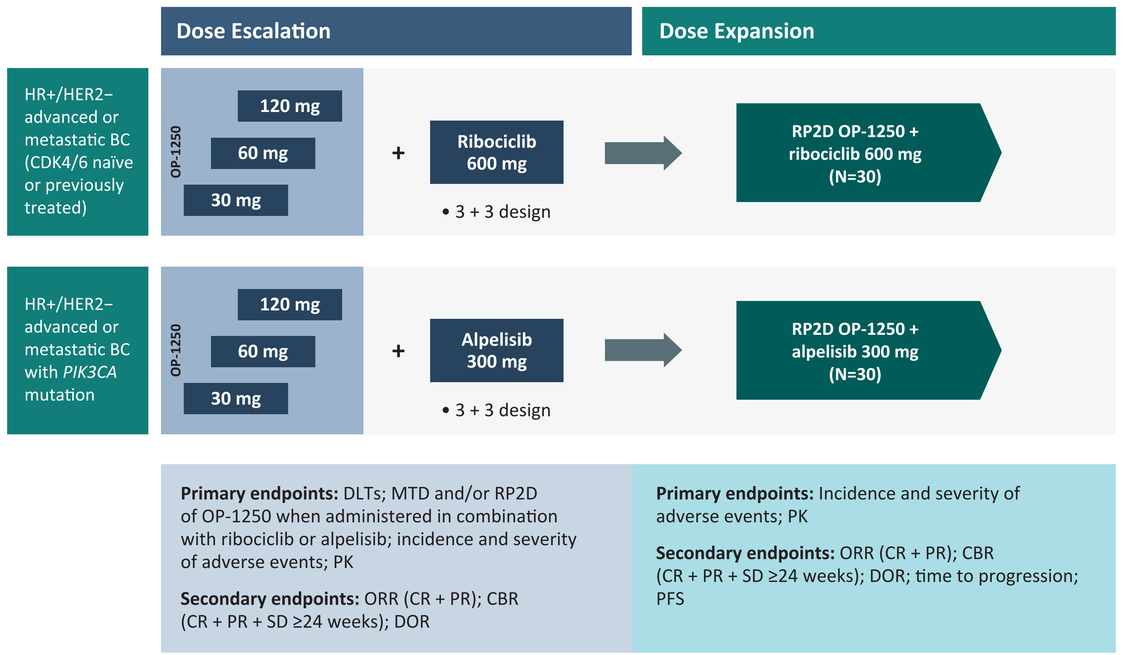
- To evaluate the safety, pharmacokinetics, and antitumor activity of daily, oral administration of OP-1250 plus ribociclib or alpelisib in patients with advanced or metastatic HR+/HER2– breast cancer

Methods

Study design

- This phase 1b, open label, two-part study (NCT05508906) is comprised of a dose-escalation phase followed by a dose-expansion phase (**Figure 3**)
  - The dose escalation cohorts will evaluate the safety and PK of oral OP-1250 (30 mg, 60 mg, or 120 mg once daily) in combination with ribociclib 600 mg once daily (cohort 1) or alpelisib 300 mg once daily (cohort 2), to identify the recommended phase 2 dose (RP2D) of OP-1250
  - The dose expansion cohorts will assess additional safety and pharmacokinetic parameters, and further explore the antitumor activity of OP-1250 (at the RP2D) in combination with ribociclib (cohort 1) or alpelisib (cohort 2)

Figure 3. OP-1250-003 study design



BC, breast cancer; **CBR**, clinical benefit rate; **CDK**, cyclin-dependent kinase; **CNS**, central nervous system; **CR**, complete response; **DLT**, dose-limiting toxicity; **DOR**, duration of response; **HER2**, human epidermal growth factor receptor 2; **HR+**, hormone receptor-positive; **MTD**, maximum tolerated dose; **ORR**, overall response rate; **PFS**, progression-free survival; ***PIK3CA***, phosphoinositide 3-kinase alpha catalytic subunit; **PK**, pharmacokinetics; **PR**, partial response; **RP2D**, recommended phase 2 dose; **SD**, stable disease.

Study Eligibility

- Key eligibility criteria are shown in **Table 1**

Table 1. Key eligibility criteria

Age ≥18 years
ECOG PS 0 or 1
Histologically or cytologically confirmed advanced or MBC with no curative treatment
HR+[a]/HER2– breast cancer
Evaluable disease (measurable per RECIST v1.1 or bone only evaluable disease)
0 to 2 prior endocrine therapies for advanced or MBC
0 to 1 prior chemotherapy for locally advanced or MBC
0 to 2 prior CDK4/6 inhibitors are permitted
Presence of *PIK3CA* mutation[b] (OP-1250 plus alpelisib group)
No prior treatment with a PI3K inhibitor (OP-1250 plus alpelisib group)
Patients with stable or treated brain metastases are eligible
Patients with endocrine-resistant[c] disease are not eligible

[a]Defined as ER+ and PR+ or PR– in the local pathology report of the most recently obtained archival tumor tissue sample from a metastatic site (unless de novo diagnosis or no metastatic biopsy undertaken).

[b]As determined by an FDA-approved alpelisib companion diagnostic test on a metastatic tissue specimen (frozen or formalin-fixed, paraffin-embedded) or in plasma (ctDNA).

[c]Defined as progression during the first 2 years of adjuvant endocrine therapy or lack of ≥6 months of continuous endocrine therapy for locally advanced or MBC.

CDK, cyclin-dependent kinase; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **ER+**, estrogen receptor-positive; **FDA**, US Food and Drug Administration; **HR+**, hormone receptor-positive (defined as ER+ and PR+ or PR–); **HER2**, human epidermal growth factor receptor 2; **MBC**, metastatic breast cancer; **PI3K**, phosphoinositide 3-kinase; ***PIK3CA***, phosphoinositide 3-kinase alpha catalytic subunit; **PR–**, progesterone receptor-negative; **PR+**, progesterone receptor-positive; **RECIST**, Response Evaluation Criteria in Solid Tumors.

Study Sites Currently Enrolling

- Enrollment is ongoing and expected at approximately 20 sites in the United States and Australia. Sites that are currently active are listed in **Table 2**

Table 2. Active study sites

Study site	Location
AdventHealth Cancer Institute	Orlando, FL, USA
University of Colorado Cancer Center	Denver, CO , USA
Vanderbilt-Ingram Cancer Center	Nashville, TN, USA
Washington University School of Medicine	St. Louis, MO, USA
Breast Cancer Research Centre - Western Australia	Nedlands, WA, Australia
Icahn School of Medicine at Mount Sinai	New York, NY, USA

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