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A phase 1/2 trial evaluating the safety, tolerability, and efficacy of the KAT6 inhibitor, PF-07248144, in combination with vepdegestrant in patients with ER+/HER2– locally advanced or metastatic breast cancer

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Objective

To evaluate the safety, tolerability (maximum tolerated dose [MTD] and recommended dose for expansion [RDE]), pharmacokinetics (PK), pharmacodynamics (PD), and anti-tumor activity of the KAT6 inhibitor PF-07248144 in combination with the PROteolysis TArgeting Chimera (PROTAC) estrogen receptor (ER) degrader vepdegestrant in an open-label, multicenter, phase 1/2 trial of patients with ER-positive/human epidermal growth factor receptor 2-negative (ER+/HER2–) locally advanced/metastatic breast cancer (aBC) who have progressed after at least 1 prior line of cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) and 1 line of endocrine therapy (ET).

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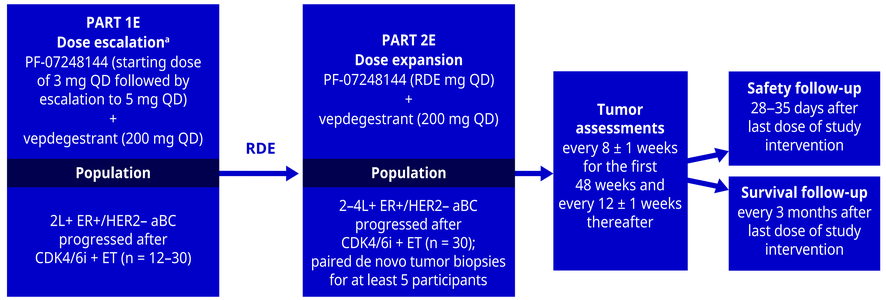
Background

- A CDK4/6i in combination with ET is the standard of care for the first-line (1L) treatment of ER+/HER2– aBC.[1,2]
- Although a CDK4/6i plus ET significantly prolongs progression-free survival (PFS) in patients with ER+/HER2– aBC, resistance ultimately occurs.[3]
- For patients who develop resistance to CDK4/6i-based therapy, there is no universal standard of care, highlighting a key unmet need for this patient population.[4]
- PF-07248144 is a novel, oral, selective inhibitor of KAT6A and KAT6B, two histone lysine acetyltransferases that regulate lineage-specific gene transcription via H3K23 acetylation.[5]
- In the ongoing phase 1/2 study C4551001, PF-07248144 5 mg QD in combination with fulvestrant has demonstrated a tolerable safety profile and durable anti-tumor activity in patients with heavily pretreated ER+/HER2– metastatic breast cancer post CDK4/6i and ET.[5]
- Vepdegestrant (ARV-471/PF-07850327) is an oral PROTAC ER degrader that has exhibited clinical activity as monotherapy in heavily pretreated patients with ER+/HER2– aBC at a recommended phase 3 dose of 200 mg QD.[6]
- Here, we describe an ongoing phase 1/2 study that aims to evaluate the safety, tolerability, and anti-tumor activity of the KAT6 inhibitor, PF-07248144, in combination with vepdegestrant in patients with ER+/HER2– aBC (NCT04606446).

Materials and methods

- This is an international (5 countries, 41 sites), phase 1/2, open-label study of PF-07248144 as a monotherapy and in combination with other agents for patients with advanced or metastatic solid tumors, including breast cancer.
- PF-07248144 combined with vepdegestrant is specifically being investigated in patients with ER+/HER2– aBC in Part 1E (dose escalation) and Part 2E (dose expansion).
- Study design and key inclusion/exclusion criteria are presented in **Figure 1**.

Figure 1. Study design



KEY INCLUSION CRITERIA

- Adults aged ≥18 years (or per local regulatory requirements)
- Histologically or cytologically confirmed ER+/HER2– aBC
- Disease progression after ≥1 prior line of treatment with CDK4/6i and ET in the advanced/metastatic setting
- For participants in Part 2E, a maximum of 3 lines of systemic therapies, including up to 1 line of cytotoxic chemotherapy for visceral disease in the advanced or metastatic setting
- Measurable disease per RECIST v1.1
- Adequate bone marrow, renal, and liver function
- Participants with asymptomatic/stable brain metastasis are allowed
- Prior treatment with fulvestrant is allowed in part 2E
- ECOG performance status 0 or 1
- Female participants must be postmenopausal; premenopausal women with ovarian suppression are allowed

KEY EXCLUSION CRITERIA

- Any other active malignancy within 3 years of study entry
- Major ECG abnormalities or cardiac disorders
- Symptomatic brain metastases requiring steroids
- Advanced/metastatic, symptomatic, visceral spread leading to risk of life-threatening complications in the short term
- Active, uncontrollable infection
- Active inflammatory gastrointestinal diseases or conditions
- Pregnancy or breastfeeding

[a]This figure represents ongoing dose levels evaluated at the time of disclosure. The protocol allows for evaluation of additional doses for both PF-07248144 and vepdegestrant based on evolving data to inform Part 2E RDE.
2L+, second-line or later; aBC, locally advanced/metastatic breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; QD, once daily; RDE, recommended dose for expansion; RECIST, Response Evaluation Criteria in Solid Tumors.

TREATMENT INTERVENTIONS

- In Part 1E, participants will self-administer a starting dose of once daily PF-07248144 3 mg in combination with once daily vepdegestrant (200 mg), orally with food and 8 oz of water, continuously on a 28-day cycle. Subsequent cohorts will receive escalating PF-07248144 doses (ie, 5 mg plus 200 mg vepdegestrant) as informed by the totality of evidence and a Bayesian Logistic Regression Model (BLRM).
- In Part 2E, participants will self-administer once daily PF-07248144 at the RDE in combination with vepdegestrant.

STUDY ENDPOINTS

Table 1. Key study endpoints

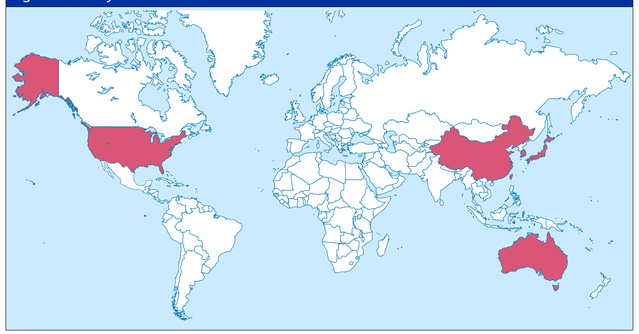
Primary	• Dose limiting toxicities (Part 1 only) • Safety • Tolerability	**Secondary**	• PK for PF-07248144 and vepdegestrant • Anti-tumor activity (Part 2 only) – BOR, DOR and CBR assessed by investigator based on RECIST v1.1 – PFS and TTP based on RECIST v1.1 – OS
Exploratory	• Anti-tumor activity (Part 1 only) – BOR, DOR and CBR assessed by investigator based on RECIST v1.1 – PFS based on RECIST v1.1 • Evaluation of key PD effects (eg, change from baseline levels of H3K23 acetylation and other downstream PD biomarkers of KAT6A/B, CDK4, and ER pathways) in pre- and on-treatment peripheral blood and/or tumor biopsies • Biomarker analyses • Patient-reported outcomes assessed using patient-reported survey (Part 2 only)		

BOR, best overall response; CBR, clinical benefit rate; CDK4, cyclin-dependent kinase 4; DOR, duration of response; ER, estrogen receptor; PFS, progression-free survival; OS, overall survival; PD, pharmacodynamics; PK, pharmacokinetics; RECIST, Response Evaluation Criteria in Solid Tumors; TTP, time to progression.

STATISTICAL CONSIDERATIONS

- No formal hypotheses will be tested in this study.
- The sample size of Part 1E will be 12–30 participants and will depend on the tolerability of PF-07248144 and the number of dose levels required to identify the MTD/RDE in combination with vepdegestrant.
- Dose escalation will be guided by a BLRM with the Escalation with Overdose Control (EWOC) principle.
- Approximately 30 participants will be enrolled in Part 2E.
- Tumor response analyses will be conducted using the safety analysis set; Kaplan–Meier methods will be used to analyze all time to event endpoints.

Figure 2. Study site locations



TRIAL ENROLLMENT INFORMATION

- Trial registration: NCT04606446
- Study start date: November 2020
- Number of enrolled patients (as of October 2025): Part 1E = 9/12–30; Part 2E = not yet open for enrollment
- Study site locations: Australia, China, Japan, Republic of Korea, United States

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