PS1-10-09

Dose optimization of PF-07248144, a first-in-class KAT6 inhibitor, in patients with ER+/HER2− metastatic breast cancer: results from phase 1 study to support the recommended phase 3 dose

Yeon Hee Park,[1] Toru Mukohara,[2] David Sommerhalder,[3] Kan Yonemori,[4] Erika Hamilton,[5] Rachel M. Layman,[6] Sung-Bae Kim,[7] Seock-Ah Im,[8] Hope S. Rugo,[9] Toshinari Yamashita,[10] Fengting Yan,[11] Fumikata Hara,[12] Gunmin Kim,[13] Shusen Wang,[14] Sean Kent,[15] Li Liu,[16] Athanasia Skoura,[17] Karey Kowalski,[16] Meng Li,[18] and Patricia M. LoRusso[19]

[1]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [2]Department of Medical Oncology, National Cancer Center Hospital East, Kashiwa, Japan; [3]NEXT Oncology, San Antonio, TX, USA; [4]Department of Medical Oncology, National Cancer Center Hospital, Tokyo, Japan; [5]Medical Oncology, Sarah Cannon Research Institute, Nashville, TN, USA; [6]Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [7]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [8]Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Cancer Research Institute, Seoul National University, Seoul, Republic of Korea; [9]Department of Medical Oncology & Therapeutics Research, City of Hope, Duarte, CA, USA; [10]Department of Breast Surgery and Oncology, Kanagawa Cancer Center, Yokohama, Japan; [11]Breast Medical Oncology, Swedish Cancer Institute, First Hill-True Family Women's Cancer Center, Seattle, WA, USA; [12]The Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan; [13]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea; [14]Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China; [15]Oncology, Pfizer Inc, Cambridge, MA, USA; [16]Oncology, Pfizer Inc, San Diego, CA, USA; [17]Oncology, Pfizer Inc, Collegeville, PA, USA; [18]Oncology, Pfizer Inc, San Francisco, CA, USA; [19]Medical Oncology, Yale School of Medicine, New Haven, CT, USA

Objective

To inform the recommended phase 3 dose (RP3D), we performed a thorough benefit–risk assessment in patients with estrogen receptor-positive (ER+)/human epidermal growth factor receptor 2-negative (HER2−) metastatic breast cancer (mBC) treated with 2 pharmacokinetically distinguishable doses of PF-07248144 in a phase 1 study (NCT04606446).

Conclusions

- 5 mg once daily (QD) PF-07248144 was identified as the RP3D in combination with fulvestrant based on pharmacokinetic (PK) exposure, maximal blood and tumor pharmacodynamic (PD) inhibition, acceptable safety, and encouraging antitumor activity.
- A pivotal phase 3 trial of PF-07248144 plus fulvestrant (NCT07062965) is ongoing to address the high unmet medical need in HR+/HER2− mBC after progression on a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor plus endocrine therapy (ET).

Presenting author: Yeon Hee Park

Email for more information: yhparkhmo@skku.edu

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References: 1. Sharma S et al. *Cell Chem Biol*. 2023;30:1191–1210. **2.** Huang F et al. *Mol Cell Biol*. 2016;36:1900–1907. **3.** Mukohara T et al. *Nat Med*. 2024;30:2242–2250. **4.** Mukohara T et al. SABCS® 2024. Poster P4-04-28.

ClinicalTrials.gov Identifier: NCT04606446

Funding source: This work was sponsored by Pfizer Inc, USA.

Acknowledgments: This study was funded by Pfizer Inc, USA. Medical writing support was provided by Diana Avery, PhD, of Oxford PharmaGenesis Inc, Wilmington, DE, USA, and was funded by Pfizer Inc, USA.

Presented at the San Antonio Breast Cancer Symposium® (SABCS) • December 9–12, 2025 • San Antonio, TX

Introduction

- Histone lysine acetyltransferases KAT6A and KAT6B regulate lineage-specific gene transcription via histone H3 lysine 23 acetylation (H3K23Ac).[1,2]
- KAT6A/B inhibition results in transcriptional downregulation of oncogenic pathways associated with cancer proliferation in ER+ breast cancer (eg, ER, cell cycle, MYC).[1]
- PF-07248144 is a first-in-class, potent, and selective inhibitor of epigenetic modifiers KAT6A and KAT6B.
- In an ongoing phase 1 study, PF-07248144 has demonstrated a tolerable safety profile and durable antitumor activity in combination with fulvestrant in patients with ER+/HER2– mBC after prior treatment with CDK4/6 inhibitor plus ET.[3,4]
  - 1 mg and 5 mg QD PF-07248144 were selected as recommended doses for expansion based on preclinical efficacious dose prediction, clinical PK/PD, and preliminary safety and efficacy from dose escalation.

Methods

STUDY DESIGN

- This first-in-human phase 1 dose escalation and expansion study is evaluating PF-07248144 (administered orally, QD, in continuous 28-day cycles) as monotherapy and in combination with fulvestrant in patients with advanced or metastatic solid tumors (NCT04606446).

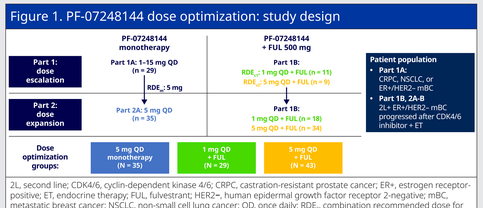
PATIENTS

- Patients were aged ≥ 18 years, had an Eastern Cooperative Oncology Group performance status of 0 or 1, and had adequate bone marrow, renal, and liver function.
- Tumor types represented in dose escalation and expansion cohorts are presented in **Figure 1**.

ASSESSMENTS

- Safety and tolerability (per Common Terminology Criteria for Adverse Events version 5.0), PK profiles, antitumor activity (per Response Evaluation Criteria in Solid Tumors version 1.1), and PD biomarkers were assessed.
- For the safety and antitumor activity outcomes reported herein from our dose optimization analysis, we used data from patients with ER+/HER2−mBC in sequential dose escalation and expansion cohorts to evaluate 2 distinguishable doses of PF-07248144 (1 mg and 5 mg QD), analyzing data from 35 patients treated with 5 mg QD PF-07248144 monotherapy, 29 patients treated with 1 mg QD PF-07248144 plus fulvestrant, and 43 patients treated with 5 mg QD PF-07248144 plus fulvestrant (**Figure 1**).

Figure 1. PF-07248144 dose optimization: study design



2L, second line; CDK4/6, cyclin-dependent kinase 4/6; CRPC, castration-resistant prostate cancer; ER+, estrogen receptor-positive; ET, endocrine therapy; FUL, fulvestrant; HER2−, human epidermal growth factor receptor 2-negative; mBC, metastatic breast cancer; NSCLC, non-small cell lung cancer; QD, once daily; RDE$_{ss}$, combination recommended dose for expansion; RDE$_{ss}$, monotherapy recommended dose for expansion.

Results

PF-07248144 PK/PD

- In dose escalation, PF-07248144 plasma exposure increased proportionally across the evaluated dose range at steady state, with low-to-moderate interpatient variability in exposure (**Figure 2A**).
  - PF-07248144 exhibited an extended plasma elimination half-life, supportive of QD dosing.
  - Dose levels of 1 mg and 5 mg QD were pharmacokinetically distinguishable, demonstrating adequate exposure separation.
- Doses of ≥ 1 mg QD PF-07248144 achieved targeted efficacious concentrations predicted by preclinical models, and no apparent PK drug interaction was observed with fulvestrant.
- In peripheral blood mononuclear cells, median H3K23Ac reduction from baseline ≥ 70% was achieved with ≥ 1 mg QD doses of PF-07248144 ± fulvestrant (**Figure 2B**).
- Paired baseline and on-treatment tumor biopsies showed that both 1 mg and 5 mg QD PF-07248144 ± fulvestrant achieved strong H3K23Ac reduction (**Figure 2C**).

PATIENTS IN DOSE OPTIMIZATION ANALYSIS

- Baseline characteristics and prior therapies for each dose optimization treatment group are reported in **Table 1**.
- All patients had ER+/HER2− mBC and previously received treatment with a CDK4/6 inhibitor plus ET in the advanced/metastatic setting.

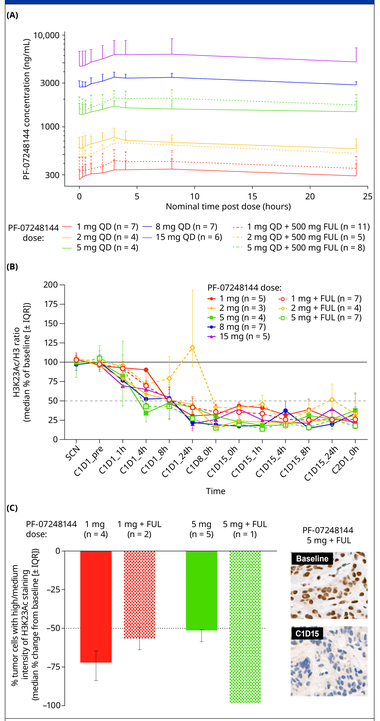
SAFETY

- Both 1 mg and 5 mg QD PF-07248144 demonstrated a tolerable safety profile when used in combination with fulvestrant (**Table 2**).
- Dysgeusia was the most common treatment-related adverse event (TRAE), which was mostly grade 1 and did not lead to any treatment discontinuations.
- The most frequent grade 3-4 TRAE was neutropenia, which was reversible and manageable with dose modifications.
- No febrile neutropenia or grade 5 TRAEs were reported.
- Among patients receiving 5 mg PF-07248144 ± fulvestrant (N = 78) who experienced a TRAE leading to dose reduction (n = 40), neutropenia was a cause of dose reduction in 32 (80.0%) patients.
- No drug-drug interactions or apparent overlapping toxicity were observed between PF-07248144 and fulvestrant.

ANTITUMOR ACTIVITY

- After a median duration of follow-up of 21.9 (95% CI, 16.5–24.8) months, durable antitumor activity was observed in patients treated with 5 mg PF-07248144 plus fulvestrant (**Figure 3A**), with an objective response rate (ORR) of 37.2% (95% CI, 23.0%–53.3%), a clinical benefit rate (CBR) of 55.8% (95% CI, 39.9%–70.9%), and a median duration of response (DOR) of 15.8 (95% CI, 9.2–not estimable) months (**Table 3**).
  - Overall, numerically higher response rates (ORR and CBR) and numerically longer median DOR were observed in the 5 mg PF-07248144 plus fulvestrant group than in the 5 mg PF-07248144 monotherapy or 1 mg PF-07248144 plus fulvestrant groups (**Table 3**).

Figure 2. PF-07248144 PK/PD when administered alone or in combination with fulvestrant: (A) mean (+ SD) plasma concentration-time profile of PF-07248144 at C1D15; (B) H3K23Ac reduction throughout C1 in PBMCs and (C) at C1D15 in tumor



C, cycle; D, day; FUL, fulvestrant; h, hour(s); H3, histone H3; H3K23Ac, histone H3 lysine 23 acetylation; IQR, interquartile range; PBMCs, peripheral blood mononuclear cells; PD, pharmacodynamics; PK, pharmacokinetics; pre, predose; QD, once daily; SCN, screening; SD, standard deviation.

Table 1. Baseline characteristics across PF-07248144 dose optimization groups

Characteristic	PF-07248144 5 mg QD (N = 35)	PF-07248144 1 mg QD + FUL 500 mg (N = 29)	PF-07248144 5 mg QD + FUL 500 mg (N = 43)
Median age (range), years	57.0 (39.0–76.0)	55.0 (32.0–88.0)	55.0 (24.0–76.0)
Primary diagnosis of ER+/HER2− breast cancer, n (%)	35 (100)	29 (100)	43 (100)
Female, n (%)	35 (100)	29 (100)	42 (97.7)
Race, n (%)			
White	9 (25.7)	3 (10.3)	13 (30.2)
Black or African American	0	0	1 (2.3)
Asian	26 (74.3)	26 (89.7)	29 (67.4)
ECOG PS, n (%)			
0	18 (51.4)	24 (82.8)	17 (39.5)
1	17 (48.6)	5 (17.2)	26 (60.5)
Mutation, n (%)			
ESR1-mut	22 (62.9)	16 (55.2)	24 (55.8)
PIK3CA/AKT1/PTEN-mut	20 (57.1)	14 (48.3)	19 (44.2)
No. of prior lines of systemic therapy in advanced/metastatic setting, median (range)	5.0 (1–13)	2.0 (1–16)	1.0 (1–6)
Prior therapy in advanced/metastatic setting, n (%)			
CDK4/6 inhibitor	35 (100)	29 (100)	43 (100)
> 12 months	19 (54.3)	15 (51.7)	33 (76.7)
ET	35 (100)	29 (100)	43 (100)
AI	30 (85.7)	27 (93.1)	38 (88.4)
Fulvestrant	28 (80.0)	5 (17.2)	5 (11.6)
Chemotherapy	26 (74.3)	14 (48.3)	12 (27.9)
Other targeted therapy	14 (40.0)	10 (34.5)	2 (4.7)

AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinase 4/6; ECOG PS, Eastern Cooperative Oncology Group performance status; ER+, estrogen receptor-positive; ET, endocrine therapy; FUL, fulvestrant; HER2−, human epidermal growth factor receptor 2-negative; mut, mutant; QD, once daily.

Table 2. TRAEs across PF-07248144 dose optimization groups

	PF-07248144 5 mg QD (N = 35)		PF-07248144 1 mg QD + FUL 500 mg (N = 29)		PF-07248144 5 mg QD + FUL 500 mg (N = 43)	
Most frequent TRAEs (≥ 20%)						
TRAE, n (%)	**All grade**	**≥ G3**	**All grade**	**≥ G3**	**All grade**	**≥ G3**
Any TRAE	33 (94.3)	18 (51.4)	27 (93.1)	7 (24.1)	43 (100)	27 (62.8)
Dysgeusia	G1: 26 (74.3) G2: 4 (11.4)	0	G1: 22 (75.9) G2: 4 (13.8)	0	G1: 24 (55.8) G2: 12 (27.9)	0
Neutropenia	24 (68.6)	G3: 12 (34.3) G4: 2 (5.7)	10 (34.5)	G3: 6 (20.7) G4: 0	28 (65.1)	G3: 17 (39.5) G4: 3 (7.0)
Anemia	16 (45.7)	3 (8.6)	8 (27.6)	1 (3.4)	19 (44.2)	7 (16.3)
Leukopenia	16 (45.7)	4 (11.4)	6 (20.7)	2 (6.9)	14 (32.6)	5 (11.6)
Thrombocytopenia	13 (37.1)	0	2 (6.9)	0	7 (16.3)	1 (2.3)
AST increased	8 (22.9)	0	2 (6.9)	0	4 (9.3)	0
Fatigue	6 (17.1)	0	2 (6.9)	0	19 (44.2)	1 (2.3)
TRAEs leading to dose reductions or discontinuations, n (%)						
Dose reductions	16 (45.7)		3 (10.3)		24 (55.8[a])	
Discontinuations	1 (2.9)		1 (3.4)		1 (2.3)	

[a]Dose reductions due to AE (≥ 3 cycles): 27.9%.
AE, adverse event; AST, aspartate aminotransferase; FUL, fulvestrant; G, grade; TRAE, treatment-related adverse event; QD, once daily.

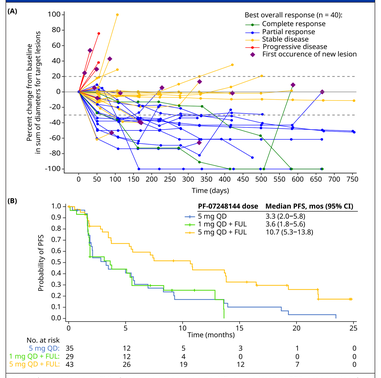
- Median progression-free survival (PFS) was 10.7 (95% CI, 5.3–13.8) months in patients treated with 5 mg PF-07248144 plus fulvestrant, compared with 3.3 (95% CI, 2.0–5.8) and 3.6 (95% CI, 1.8–5.6) months in patients treated with 5 mg PF-07248144 monotherapy or 1 mg PF-07248144 plus fulvestrant, respectively (**Figure 3B**).

Table 3. Clinical antitumor activity across PF-07248144 dose optimization groups

	PF-07248144 5 mg QD (N = 35)	PF-07248144 1 mg QD + FUL 500 mg (N = 29)	PF-07248144 5 mg QD + FUL 500 mg (N = 43)
Median follow-up, mos 95% CI	NE NE–NE	11.0 9.1–NE	21.9 16.5–24.8
ORR (CR + PR), n (%) 95% CI	4 (11.4) 3.2–26.7	7 (24.1) 10.3–43.5	16 (37.2) 23.0–53.3
Median DOR, mos 95% CI	12.0 7.4–NE	4.6 3.4–NE	15.8 9.2–NE
CBR (CR + PR + SD > 24 weeks), n (%) 95% CI	11 (31.4) 16.9–49.3	11 (37.9) 20.7–57.7	24 (55.8) 39.9–70.9
Median PFS, mos 95% CI	3.3 2.0–5.8	3.6 1.8–5.6	10.7 5.3–13.8

CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DOR, duration of response; FUL, fulvestrant; mos, months; NE, not estimable; ORR, objective response rate; PFS, progression-free survival; PR, partial response; QD, once daily; SD, stable disease.

Figure 3. Antitumor activity in PF-07248144 dose optimization groups: (A) spider plot of tumor size change from baseline for patients receiving 5 mg QD PF-07248144 + fulvestrant; (B) Kaplan–Meier plot of PFS



CI, confidence interval; FUL, fulvestrant; mos, months; NE, not estimable; PFS, progression-free survival; QD, once daily.

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