

First-in-human phase 1/2a study of the first-in-class, next-generation CDK4-selective inhibitor PF-07220060 + endocrine therapy: updated safety data in patients with HR+/HER2– mBC

Objective



To evaluate the safety and tolerability of PF-07220060 + ET in patients with HR+/HER2– mBC included in the dose-finding (Parts 1B-C) and dose-expansion (Parts 2B-C) cohorts of the first-in-human trial.

Conclusions



- PF-07220060 + ET was well tolerated in patients with HR+/HER2– mBC across post-CDK4/6i and CDK4/6i-naïve cohorts.
- At the 300 mg BID dose, the incidence of treatment-related grade ≥3 neutropenia and other treatment-related TEAEs was low, enabling high RDI (relative dose intensity) and potential for continuous target coverage.

*Presenting author: Antonio Giordano



Email for more information: Antonio_Giordano@dfci.harvard.edu



An electronic version of this poster may be obtained by scanning this Quick Response (QR) Code with your smartphone app. Copies of this poster obtained through QR code are for personal use only and may not be reproduced without permission from ASCO® or the authors of this poster.

Funding source: Study sponsored by Pfizer Inc.

References: 1. Yap et al. *J Clin Oncol*. 2023;41(16_suppl):3009.

Acknowledgments: Medical writing, conducted in accordance with Good Publication Practice (GPP 2022) and the International Committee of Medical Journal Editors (ICMJE) guidelines, was provided by Dominique J. Verlaan, PhD, of Oxford PharmaGenesis Inc., Newtown, PA, USA, with funding provided by Pfizer Inc.

Presented at the American Society of Clinical Oncology (ASCO) Meeting • May 31–June 4, 2024 • Chicago, IL

Antonio Giordano^{1*}, Manish R. Sharma², Anja Williams³, Peter Schmid⁴, Diana Fabiola Flores Diaz⁵, Manuel Magallanes⁶, Binghe Xu⁷, Min Yan⁸, Sacha J. Howell⁹, Erika Hamilton¹⁰, Cynthia Basu¹¹, Jennifer Park¹¹, Heather Neumann¹¹, Maria Delioukina¹¹, and Timothy A. Yap¹²

Introduction

- PF-07220060 is a novel, oral, and highly selective cyclin-dependent kinase 4 (CDK4) inhibitor with CDK6 sparing.
- Preliminary data from the first-in-human trial of PF-07220060 has shown antitumor activity and encouraging tolerability in patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2–) metastatic breast cancer (mBC) who had progressed on prior CDK4/6 inhibitors (CDK4/6i) + endocrine therapy (ET).¹

Methods

STUDY DESIGN AND TREATMENTS

- This is an ongoing phase 1/2a (NCT04557449), open label, multicenter, multiple dose study evaluating the safety, tolerability, pharmacokinetics, and pharmacodynamics of PF-07220060 administered as a single agent and in combination with ET (letrozole [LET] or fulvestrant [FUL]) or enzalutamide in patients with metastatic or advanced solid tumors (**Figure 1**).

- In Parts 1B and 1C, PF-07220060 + ET (LET or FUL) was administered to patients with HR+/HER2– mBC as ≥2L therapy after prior CDK4/6i.
- In Part 2B, patients with HR+/HER2– mBC who were treatment naïve received 1L PF-07220060 + LET.
- In Part 2C, patients with HR+/HER2– mBC who had progressed on prior ET (CDK4/6i naïve) received PF-07220060 + FUL.
- Other inclusion criteria include ECOG PS of 0 or 1, and adequate bone marrow, renal, and liver function.

SAFETY AND TOLERABILITY ASSESSMENTS

- Incidence and severity of adverse events (AEs) were evaluated at every visit. Investigators graded AEs as per National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0).
- Relative dose intensity (RDI) was calculated as the ratio of actual dose intensity to planned dose intensity (mg/day).

Results

PATIENTS

- At data cutoff (March 4, 2024),
 - Parts 1B-C: 33 patients received 300 mg (n=19) or 400 mg (n=14) BID PF-07220060 + ET (FUL or LET)
 - Part 2B: 34 patients received 300 mg BID PF-07220060 + LET
 - Part 2C: 39 patients received 300 mg BID PF-07220060 + FUL
- Median age of cohorts ranged from 55 to 62 years (range, 30–84); all patients were women and more than half had ECOG PS 1 (**Table 1**). The majority of women were White, although 30.8% of patients in Part 2C did not report their race.
- Patients in Parts 1B-C had a median of 4 lines of prior therapy in the advanced/metastatic setting, while patients in Part 2B had none and patients in Part 2C had 1.

Table 1. Demographic and baseline characteristics			
	Parts 1B-C 300/400 mg BID PF-07220060 + LET/FUL (N=33)	Part 2B 300 mg BID PF-07220060 + LET (N=34)	Part 2C 300 mg BID PF-07220060 + FUL (N=39)
Median age (range), y	62.0 (41–82)	59.0 (32–84)	55.0 (30–76)
Female sex, n (%)	33 (100)	34 (100)	39 (100)
Race, n (%)			
White	22 (66.7)	23 (67.6)	12 (30.8)
Black or African American	1 (3.0)	0	0
Asian	1 (3.0)	8 (23.5)	9 (23.1)
American Indian/Alaska Native	0	2 (5.9)	6 (15.4)
Not reported	9 (27.3)	1 (2.9)	12 (30.8)
ECOG PS, n (%)			
0	12 (36.4)	15 (44.1)	13 (33.3)
1	21 (63.6)	19 (55.9)	26 (66.7)
Prior anticancer surgery, n (%)	27 (81.8)	19 (55.9)	30 (76.9)
Median number of prior systemic lines in advanced/metastatic setting (range)	4.0 (1–11)	0 (0–0)	1.0 (0–3)
Prior CDK4/6 inhibitor, n (%)	33 (100)	0	0
Prior fulvestrant, n (%)	24 (72.7)	0	0
Prior chemotherapy, n (%)	22 (66.7)	0	8 (20.5)
BID, twice daily; CDK4/6, cyclin-dependent kinase 4/6; ECOG PS, Eastern Cooperative Oncology Group performance status; FUL, fulvestrant; LET, letrozole.			

SAFETY AND TOLERABILITY

Parts 1B-C cohort (300/400 mg BID PF-07220060 + LET/FUL)

- The most common treatment-related treatment-emergent adverse events (TEAEs) were neutropenia (54.5%), diarrhea (42.4%), and nausea (36.4%) (**Table 2**).
- The most common grade 3 treatment-related TEAEs were neutropenia (18.2%), leukopenia (9.1%), and anemia (9.1%). No grade ≥4 treatment-related TEAEs occurred, and no febrile neutropenia was observed.
- A grade 3 treatment-related serious AE (SAE) of nausea occurred in 1 patient (3.0%).
- One patient (3.0%) discontinued PF-07220060 due to treatment-related grade 3 TEAEs of leukopenia and recurrent neutropenia.
- Treatment-related TEAEs led to PF-07220060 dose interruption in 10 patients (30.3%) and dose reduction in 5 patients (15.2%).
- Median RDI (range) of PF-07220060 was 97.9% (52.5–100), and 81.8% of patients received RDI >80%.

Part 2B cohort (300 mg BID PF-07220060 + LET)

- The most common treatment-related TEAEs were neutropenia (61.8%), leukopenia (38.2%), and anemia (20.6%) (**Table 3**).
- The most common grade 3 treatment-related TEAEs were neutropenia (23.5%) and gamma-glutamyltransferase increased (5.9%). No grade ≥4 treatment-related TEAEs occurred, and no febrile neutropenia was observed.
- Treatment-related SAEs were hypokalemia (grade 3) and interstitial lung disease (grade 3), which occurred in 1 patient each (2.9%).
- One patient (2.9%) discontinued PF-07220060 due to a treatment-related TEAE (aspartate aminotransferase increased; grade 3).
- Treatment-related TEAEs led to PF-07220060 dose interruption in 13 patients (38.2%) and dose reduction in 3 patients (8.8%).
- Median RDI (range) of PF-07220060 was 99.1% (36.0–100), and 91.2% of patients received RDI >80%.

Part 2C cohort (300 mg BID PF-07220060 + FUL)

- The most common treatment-related TEAEs were neutropenia (38.5%), leukopenia (33.3%), and anemia (25.6%) (**Table 4**).
- The most common grade 3 treatment-related TEAEs were neutropenia (12.8%), leukopenia (12.8%), and lymphopenia (7.7%). No grade ≥4 treatment-related TEAEs occurred, and no febrile neutropenia was observed.
- A grade 2 treatment-related SAE of chronic gastritis occurred in 1 patient (2.6%).
- No patients discontinued PF-07220060 due to treatment-related TEAEs.
- Treatment-related TEAEs led to PF-07220060 dose interruption in 9 patients (23.1%) and dose reduction in 4 patients (10.3%).
- Median RDI (range) of PF-07220060 was 99.6% (68.6–100), and 92.3% of patients received RDI >80%.

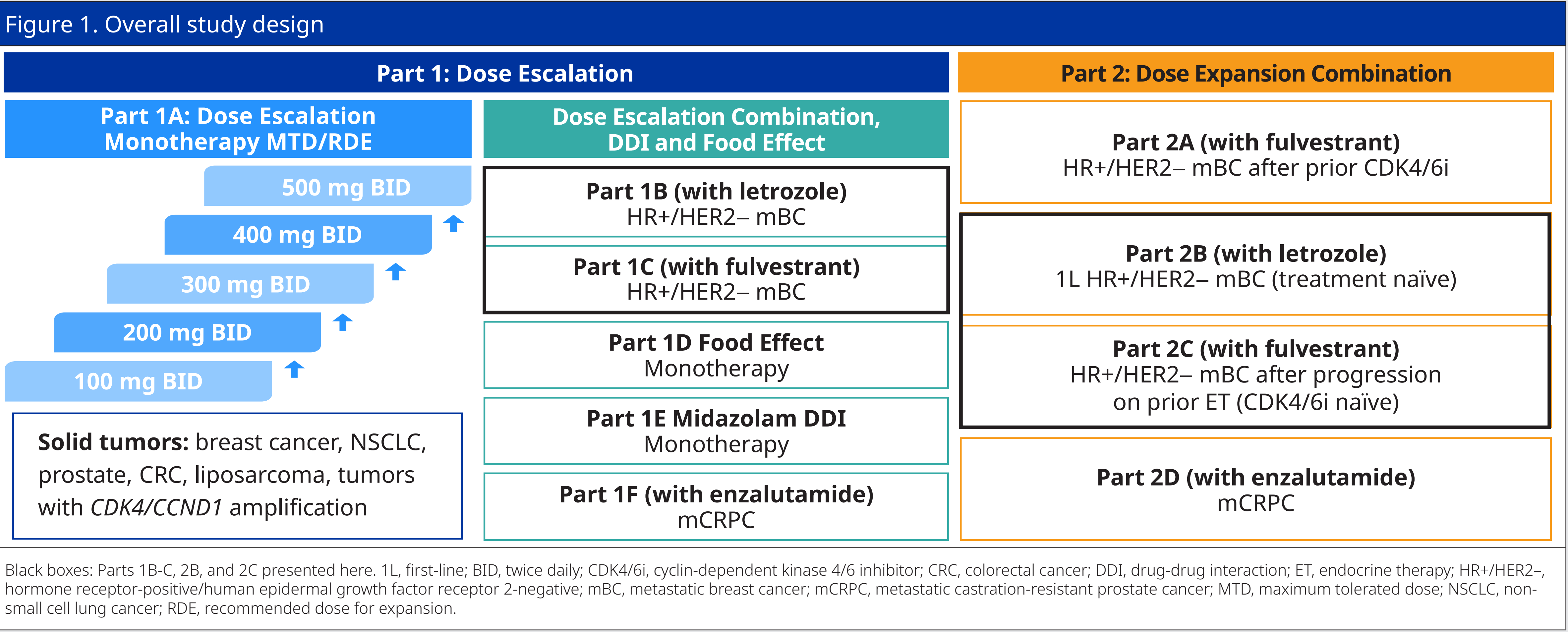


Table 2. Parts 1B-C: treatment-related TEAEs occurring in ≥10% of patients by maximum grade				
AEs by MedDRA PT, n (%)	Grade 1	Grade 2	Grade 3*	Total (n=33)
Any	11 (33.3)	10 (30.3)	11 (33.3)	32 (97.0)
Neutropenia	5 (15.2)	7 (21.2)	6 (18.2)	18 (54.5)
Diarrhea	13 (39.4)	1 (3.0)	0	14 (42.4)
Nausea	9 (27.3)	2 (6.1)	1 (3.0)	12 (36.4)
Leukopenia	4 (12.1)	3 (9.1)	3 (9.1)	10 (30.3)
Thrombocytopenia	9 (27.3)	0	1 (3.0)	10 (30.3)
Fatigue	8 (24.2)	1 (3.0)	0	9 (27.3)
Anemia	3 (9.1)	1 (3.0)	3 (9.1)	7 (21.2)
Arthralgia	5 (15.2)	1 (3.0)	0	6 (18.2)
Vomiting	4 (12.1)	1 (3.0)	0	5 (15.2)
Alopecia	4 (12.1)	0	0	4 (12.1)
Hot flush	4 (12.1)	0	0	4 (12.1)

*No grade ≥4 treatment-related TEAEs occurred.
AE, adverse event; MedDRA PT, Medical Dictionary for Regulatory Activities preferred term; TEAE, treatment-emergent adverse event.

Table 3. Part 2B: treatment-related TEAEs occurring in ≥10% of patients by maximum grade				
AEs by MedDRA PT, n (%)	Grade 1	Grade 2	Grade 3*	Total (n=34)
Any	4 (11.8)	11 (32.4)	13 (38.2)	28 (82.4)
Neutropenia	3 (8.8)	10 (29.4)	8 (23.5)	21 (61.8)
Leukopenia	3 (8.8)	10 (29.4)	0	13 (38.2)
Anemia	6 (17.6)	1 (2.9)	0	7 (20.6)
Lymphopenia	2 (5.9)	4 (11.8)	1 (2.9)	7 (20.6)
Alopecia	4 (11.8)	0	0	4 (11.8)
Alpha-hydroxybutyrate dehydrogenase increased	4 (11.8)	0	0	4 (11.8)
Blood lactate dehydrogenase increased	4 (11.8)	0	0	4 (11.8)
Gamma-glutamyltransferase increased	2 (5.9)	0	2 (5.9)	4 (11.8)
Hyperglycemia	4 (11.8)	0	0	4 (11.8)
Hypermagnesemia	4 (11.8)	0	0	4 (11.8)
Thrombocytopenia	4 (11.8)	0	0	4 (11.8)

*No grade ≥4 treatment-related TEAEs occurred.
AE, adverse event; MedDRA PT, Medical Dictionary for Regulatory Activities preferred term; TEAE, treatment-emergent adverse event.

Table 4. Part 2C: treatment-related TEAEs occurring in ≥10% of patients by maximum grade				
AEs by MedDRA PT, n (%)	Grade 1	Grade 2	Grade 3*	Total (n=39)
Any	4 (10.3)	14 (35.9)	9 (23.1)	27 (69.2)
Neutropenia	1 (2.6)	9 (23.1)	5 (12.8)	15 (38.5)
Leukopenia	4 (10.3)	4 (10.3)	5 (12.8)	13 (33.3)
Anemia	5 (12.8)	4 (10.3)	1 (2.6)	10 (25.6)
Lymphopenia	1 (2.6)	4 (10.3)	3 (7.7)	8 (20.5)
Diarrhea	4 (10.3)	3 (7.7)	0	7 (17.9)
Thrombocytopenia	6 (15.4)	1 (2.6)	0	7 (17.9)
Nausea	5 (12.8)	1 (2.6)	0	6 (15.4)
Aspartate aminotransferase increased	4 (10.3)	1 (2.6)	0	5 (12.8)
Alanine aminotransferase increased	4 (10.3)	0	0	4 (10.3)
Alopecia	4 (10.3)	0	0	4 (10.3)
Alpha-hydroxybutyrate dehydrogenase increased	4 (10.3)	0	0	4 (10.3)
Gamma-glutamyltransferase increased	2 (5.1)	1 (2.6)	1 (2.6)	4 (10.3)
Sinus bradycardia	4 (10.3)	0	0	4 (10.3)

*No grade ≥4 treatment-related TEAEs occurred.
AE, adverse event; MedDRA PT, Medical Dictionary for Regulatory Activities preferred term; TEAE, treatment-emergent adverse event.