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The next-generation CDK4-selective inhibitor atirmociclib (PF-07220060) in combination with letrozole as first-line treatment in patients with HR+/HER2– metastatic breast cancer

Antonio Giordano,[1] Manuel Magallanes,[2] Binghe Xu,[3] Diego Kaen,[4] Ernesto Korbenfeld,[5] Min Yan,[6] Omar Zayas Villanueva,[7] Carlos Alberto Hernandez,[8] Peter Schmid,[9] Michal Mego,[10] Santiago Bella,[11] Xinhong Wu,[12] Feng Liu,[13] Cynthia Basu,[13] Jennifer Park,[13] Heather Neumann,[13] Maria Delioukina,[13] Timothy A. Yap[14]

[1]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [2]Centro Oncologico Internacional, Mexico City, Mexico; [3]National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [4]Fundación CORI para la Investigación y Prevención del Cáncer, La Rioja, Argentina; [5]Hospital Británico de Buenos Aires, Buenos Aires, Argentina; [6]The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, China; [7]Hospital Universitario "Dr. Jose Eleuterio Gonzalez", Monterrey, Mexico; [8]Hospital Regional Presidente Juárez, Institute for Social Security and Services for State Workers, Oaxaca, Mexico; [9]Barts Cancer Institute, Queen Mary University of London, London, UK; [10]Narodny onkologicky ustav, Bratislava, Slovakia; [11]Clinica Universitaria Reina Fabiola, Cordoba, Argentina; [12]Department of Breast Surgery, Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology, Hubei Provincial Clinical Research Center for Breast Cancer, Wuhan Clinical Research Center for Breast Cancer, Wuhan, Hubei, China; [13]Pfizer Inc, La Jolla, CA, USA; [14]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Objective

To evaluate the safety, tolerability and efficacy of atirmociclib plus letrozole in treatment-naïve patients with HR+/HER2– metastatic breast cancer (mBC) in an ongoing phase 1/2a study (cohort 2B).

Conclusions

- Preliminary findings of atirmociclib + letrozole combination treatment showed favorable safety and tolerability and promising anti-tumor activity (confirmed objective response [OR] rate in patients with measurable disease at baseline: 61%), irrespective of *PIK3CA/AKT1/PTEN* mutations, in treatment-naïve patients with HR+/HER2– mBC.
- At the recommended phase 3 atirmociclib dose of 300 mg BID, high (> 90%) relative dose intensity was achieved in 85% of patients, potentially ensuring higher anti-cancer activity.
- At the atirmociclib 300 mg BID dose, the incidence of treatment-related Grade ≥ 3 neutropenia and other treatment-related adverse events (TRAEs) was low; no grade 4/5 TRAEs were observed.

Presenting author: Antonio Giordano

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

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Introduction

- Atirmociclib (PF-07220060) is a next-generation, highly selective and potent cyclin-dependent kinase (CDK) 4 inhibitor with significant sparing of CDK6.[1,2]
- Preliminary data from an ongoing phase 1/2a study (NCT04557449) indicate atirmociclib combined with endocrine therapy (ET) has a favorable safety profile and promising anti-tumor activity in patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2–) metastatic breast cancer (mBC) who progressed on a prior CDK4/6 inhibitor.[1,2]
- Compared with CDK4/6 inhibitors, atirmociclib may clinically exhibit a wider safety and tolerability margin for neutropenia, as suggested in preclinical in vivo models,[3,4] and thereby, additionally exhibit greater anti-tumor activity by allowing for higher dosing to attain tolerated plasma concentrations.
- In this ongoing phase 1/2a study, the safety, tolerability, and efficacy of atirmociclib plus letrozole was investigated in an expansion cohort of patients untreated (treatment-naïve) for their advanced mBC; preliminary findings are first reported here.

Methods

STUDY DESIGN AND TREATMENTS

- This is an ongoing phase 1/2a open label, multicenter, multiple dose study evaluating the safety, tolerability, pharmacokinetics and pharmacodynamics of atirmociclib administered as a single agent and in combination with ET (letrozole or fulvestrant) in patients with metastatic or advanced solid tumors.
- Participants ≥ 18 years of age with HR+/HER2– mBC who were treatment-naïve for their advanced disease were enrolled in cohort 2B.
  - Other inclusion criteria included measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, and Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
- Participants were excluded if they had prior treatment with any CDK4/6 inhibitor; or had disease recurrence while on or within 12 months of prior (neo)adjuvant treatment with an aromatase inhibitor.
- In part 2B, patients received fist-line (1L) atirmociclib (300 mg BID) + letrozole (2.5 mg orally QD).

SAFETY AND TOLERABILITY ASSESSMENTS

- The primary objective in cohort 2B was to assess the safety and tolerability of atirmociclib + letrozole.
- 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.

EFFICACY ASSESSMENTS

- Secondary objectives were to evaluate the anti-tumor activity of atirmociclib + letrozole, duration of response (DOR) and progression-free survival (PFS).
- Anti-tumor activity was measured by investigator-assessed confirmed OR rate, defined as the proportion of patients with complete response (CR) or partial response (PR), and clinical benefit rate (CBR), defined as OR or ≥ 24 weeks with stable disease.
- Radiological tumor assessments were conducted at baseline, during treatment (every 8 weeks from start of treatment for first 6 months; then, every 12 weeks [±7 days] for up to 2 years; after 2 years, every 4 months [±14 days]) and at the time of withdrawal from treatment by investigators using RECIST v1.1.
- PFS was defined as the time from first dose until date of first documentation of disease progression or death due to any cause.
- Genomic alterations in circulating tumor DNA (ctDNA) were determined using the next-generation sequencing assays (Guardant360 platform or PredicineCARE [Chinese participants only]).

STATISTICAL ANALYSES

- Descriptive statistics were used to summarize patient demographics and characteristics at baseline, AEs, dose modifications and treatment response.
- Kaplan–Meier estimation was used to describe follow-up duration and PFS.
- Exact 95% confidence intervals (CIs) for binomial proportions of response rates were calculated using the Clopper–Pearson method.

Results

PATIENTS

- At the data cutoff of July 11, 2024, 34 patients had received atirmociclib + letrozole. Median age was 59 years; 67.6% were White and 23.5% were Asian. Most (55.9%) had an ECOG performance status of 1 (**Table 1**).
- In this cohort of patients who had not received any prior systemic anticancer therapies in the advanced metastatic setting, 55.9% (n = 19) had undergone prior surgery and 47.1% (n = 16) had prior adjuvant/neoadjuvant therapy.
- Median duration of follow-up was 16.5 months (95% CI, 14.1–19.4).

Table 1. Patient demographics and characteristics

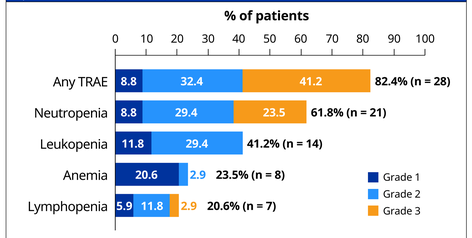
Characteristic	Cohort 2B (n = 34)
Age at screening, years	
Mean (SD)	58.6 (13.0)
Median (range)	59 (32–84)
Age group	
18–44 years	5 (14.7)
45–64 years	18 (52.9)
≥ 65 years	11 (32.4)
Female sex	34 (100)
Race	
White	23 (67.6)
Asian	8 (23.5)
Black	0
American Indian or Alaskan Native	2 (5.9)
Not reported	1 (2.9)
Ethnicity	
Hispanic or Latino	22 (64.7)
Not Hispanic or Latino	12 (35.3)
ECOG performance status	
0	15 (44.1)
1	19 (55.9)

Data presented as n (%) unless indicated otherwise.
ECOG, Eastern Cooperative Oncology Group; SD, standard deviation.

SAFETY AND TOLERABILITY

- TRAEs occurred in 28 patients (82.4%); 41.2% (14/34) had Grade 3 TRAEs and no patients had Grade 4 or 5 TRAEs (**Figure 1**).
  - The most common TRAEs were neutropenia (61.8% [21/34]; 23.5% [8/34] Grade 3), leukopenia (41.2%; no Grade 3), anemia (23.5%; no Grade 3), and lymphopenia (20.6%; 2.9% [1/34] Grade 3).
  - Two patients (5.9%) had a serious TRAE; one was Grade 3 hypokalemia and the other was Grade 3 interstitial lung disease (ILD).
  - Serious Grade 3 ILD was the only ILD AE/serious AE reported; 1/34 participant (2.9%) reported Grade 1 diarrhea.

Figure 1. Proportion of patients with TRAEs by maximum grade (occurring in ≥ 20% of patients; n = 34)



TRAE, treatment-related adverse event.

- Due to a TRAE, 1 patient (2.9%) discontinued atirmociclib, 3 (8.8%) had dose reductions and 13 (38.2%) had dose interruptions.
- Median RDI of atirmociclib was 99.3% (range 35.4–100); 85.3% (29/34) of patients had RDI > 90%.

EFFICACY

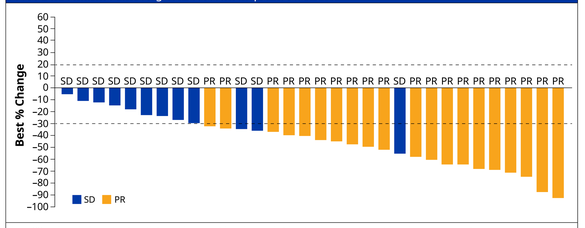
- Confirmed OR rate was 58.8% (20/34), all were PRs (**Table 2**).
  - The CBR was 94.1% (32/34).
  - Median time to response was 3.7 months (range, 1.6–15.6).
  - Median duration of confirmed response was not reached.
- Among the 33 patients with measurable disease at baseline, the confirmed OR rate and CBR were 60.6% and 93.9%, respectively.
- Confirmed OR rate and CBR were largely independent of *PIK3CA/AKT1/PTEN* gene mutations.
- With a median duration of follow-up of 16.5 months, median PFS has not been reached.
  - At data cutoff, 25 of 34 patients continued treatment without progression.
- The depth and duration of tumor responses to atirmociclib + letrozole are illustrated in the waterfall plot in **Figure 2** and spider plot in **Figure 3**.

Table 2. Confirmed tumor response based on investigator assessment (RECIST v1.1)

	Total	*PIK3CA, AKT1* or *PTEN* mutations* (≥ 1)	
		Yes	No
Best overall response	**n = 34**	**n = 13**	**n = 15**
Complete response (CR)	0	0	0
Partial response (PR)	20 (58.8)	8 (61.5)	8 (53.3)
Stable disease (SD)	12 (35.3)	4 (30.8)	6 (40.0)
Progressive disease (PD)	0	0	0
Non-CR/non-PD	1 (2.9)	0	1 (6.7)
Not evaluable	1 (2.9)	1 (7.7)	0
Objective response (OR) rate (CR + PR) (95% CI)	20 (58.8) (40.7–75.4)	8 (61.5) (31.6–86.1)	8 (53.3) (26.6–78.7)
Clinical benefit rate (OR or ≥ 24 weeks SD) (95% CI)	32 (94.1) (80.3–99.3)	11 (84.6) (54.6–98.1)	15 (100) (78.2–100)
Patients with measurable disease at baseline	**n = 33**	**n = 13**	**n = 14**
OR rate (CR + PR) (95% CI)	20 (60.6) (42.1–77.1)	8 (61.5) (31.6–86.1)	8 (57.1) (28.9–82.3)
Clinical benefit rate (OR or ≥ 24 weeks SD) (95% CI)	31 (93.9) (79.8–99.3)	11 (84.6) (54.6–98.1)	14 (100) (76.8–100)

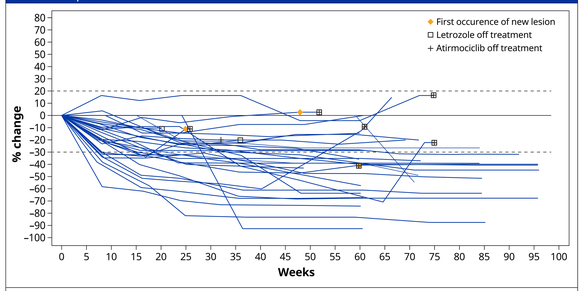
Data presented as n (%).
95% CIs based on Clopper–Pearson method.
*Any missense, nonsense or frameshift mutations as determined by Guardant360 or PredicineCARE (Chinese participants only) assay in Cycle 1 Day 1 ctDNA.
CI, confidence interval; ctDNA, circulating tumor DNA; RECIST, Response Evaluation Criteria in Solid Tumors v1.1.

Figure 2. Waterfall plot of best percent change from baseline in sum of diameters of target lesions* based on confirmed investigator assessment per RECIST v1.1



* n = 32; only includes patients with target lesions at baseline and at least one adequate post-baseline assessment.
PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Figure 3. Spider plot of tumor size change from baseline over time* based on confirmed investigator assessment per RECIST v1.1



*n = 32; only includes patients with target lesions at baseline and at least one adequate post-baseline assessment.
RECIST, Response Evaluation Criteria in Solid Tumors.

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