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Long-term safety and efficacy of first-line next generation CDK4-selective inhibitor atirmociclib + letrozole for the treatment of patients with HR+/HER2− metastatic breast cancer

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Objectives

To evaluate the long-term safety, tolerability, and efficacy of atirmociclib + letrozole in treatment-naïve patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2–) advanced/metastatic breast cancer (a/mBC) in an ongoing phase 1/2a study.

Conclusion

- At 24.8 months of follow-up, atirmociclib + letrozole continues to show favorable safety and tolerability and promising antitumor efficacy (confirmed objective response rate [cORR] of 69.7% in patients with measurable disease at baseline) when used as first-line (1L) treatment in patients with HR+/HER2− a/mBC.
- At the atirmociclib 300 mg twice daily (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.
- A randomized phase 3 trial of 1L atirmociclib + letrozole in patients with HR+/HER2− a/mBC has been initiated based on these data.

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Poster

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Abstract PLS

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Background

- Cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) + endocrine therapy (ET) are standards of care for patients with HR+/HER2− a/mBC.[1]
- Despite improvements in progression-free survival (PFS) and overall survival, patients with HR+/HER2− a/mBC often develop acquired resistance to CDK4/6i.[2]
- The anticancer effects of CDK4/6i are thought to be driven primarily by CDK4 inhibition, while CDK6 inhibition may underlie some of the toxicity observed with CDK4/6i, such as neutropenia.[3]
- Atirmociclib (PF-07220060) is a highly selective and potent oral CDK4i, sparing other CDKs such as CDK6.[3]
- Preliminary clinical data have demonstrated promising antitumor activity and favorable safety and tolerability with atirmociclib + letrozole.[4]

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 in patients with metastatic or advanced solid tumors (NCT04557449).
- Adults (≥ aged 18 years) with HR+/HER2− a/mBC who were treatment-naïve for their advanced disease were enrolled in cohort 2B and received atirmociclib (300 mg BID) + letrozole (2.5 mg orally once daily).
- Other inclusion criteria included measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and ECOG performance status of 0 or 1.
- Patients were excluded if they had prior treatment with any CDK4/6i, or had disease recurrence while on or within 12 months of prior (neo)adjuvant treatment with an aromatase inhibitor.

ASSESSMENTS

- The primary objective was to assess the safety and tolerability of atirmociclib + letrozole; secondary objectives included antitumor activity, duration of response (DOR), and PFS.
- Incidence and severity of adverse events (AEs) were assessed at every visit by investigators based on the 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.
- Antitumor activity was measured by investigator-assessed cORR, defined as the proportion of patients with complete response (CR) or partial response (PR), and clinical benefit rate (CBR), defined as CR/PR or ≥ 24 weeks with stable disease.
- PFS was defined as the time from first dose until date of first documentation of disease progression or death due to any cause.

STATISTICAL ANALYSIS

- Patient demographics and characteristics at baseline, AEs, dose modifications, and treatment response were summarized descriptively.
- 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 data cutoff (February 21, 2025), 34 patients had received 1L atirmociclib + letrozole.
- At baseline, median age was 59.0 years (range, 32–84); half of patients had undergone prior anticancer surgery, and 47.1% had received prior (neo)adjuvant therapy (**Table 1**).
- Median duration of treatment was 23.4 months.

SAFETY AND TOLERABILITY

- TRAEs occurred in 28 patients (82.4%); 47.1% (16/34) had Grade 3 TRAEs, and none had Grade 4 or 5 TRAEs (**Figure 1**).
  - The most common TRAEs were neutropenia (61.8% [21/34]; 26.5% [9/34] Grade 3) and leukopenia (41.2% [14/34]; no Grade 3).
  - No TRAEs of diarrhea of any grade were reported.
- Two patients (5.9%) had a serious TRAE; one had Grade 3 hypokalemia, and the other had Grade 3 interstitial lung disease (ILD).
- Only 1 patient (2.9%) discontinued atirmociclib due to a TRAE (Grade 3 aspartate aminotransferase increased).
- Median time to first onset of any grade neutropenia (n = 21) was 16 days (range, 1–194), with a median duration of 69 days (range, 12–611).
  - Median time to first onset of Grade 3 neutropenia (n = 9) was 31 days (range, 16–645), with a median duration of 7 days (range, 3–19).
- AEs (all causality) led to ≥ 1 atirmociclib dose interruption in 20 patients (58.8%), most often starting in the first 6 cycles (n = 14; 41.2%). Median time to first interruption was 108 days.
  - Neutropenia and ILD were the only AEs resulting in dose interruption in ≥ 2 patients.
- AEs (all causality) led to a single atirmociclib dose reduction in 6 patients (17.6%): 2 in cycles 3–6, 1 in cycles 7–12, 2 in cycles 13–24, and 1 in cycles ≥ 25. Median time to first reduction was 365 days.
- Median RDI of atirmociclib was 98.8% (range, 34.5–100); 82.4% (28/34) of patients had RDI > 90%.

EFFICACY

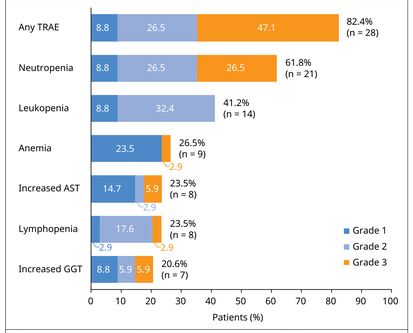
- cORR was 67.6% (23/34); all were PRs (**Table 2**).
  - CBR was 94.1% (32/34)
  - Median time to response was 5.4 months (range, 1.6–22.1)
  - Median DOR was not reached
- Among the 33 patients with measurable disease at baseline, the cORR was 69.7% and the CBR was 93.9%.
- At a median follow-up duration of 24.8 months (95% CI, 22.0–25.8), median PFS was not reached.
  - Probability of being event-free was 90.9% at 12 months, 78.4% at 18 months, and 67.2% at 24 months.
- The magnitude and duration of tumor responses to atirmociclib + letrozole are illustrated in **Figure 2**.

Table 1. Patient Demographics and Characteristics

Characteristics	Cohort 2B (n = 34)
Age at screening, years	
Mean (SD)	58.6 (13.0)
Median (range)	59 (32–84)
Female sex, n (%)	34 (100)
Pre/perimenopausal	6 (17.6)
Postmenopausal	28 (82.4)
Race, n (%)	
White	23 (67.6)
Asian	8 (23.5)
Black	0
American Indian or Alaskan Native	2 (5.9)
Not reported	1 (2.9)
Hispanic or Latino, n (%)	22 (64.7)
ECOG performance status, n (%)	
0	15 (44.1)
1	19 (55.9)
Prior anticancer surgery, n (%)	17 (50.0)
Prior (neo)adjuvant therapy, n (%)	16 (47.1)
Chemotherapy in adjuvant setting, n (%)	13 (38.2)
Visceral disease, n (%)	30 (88.2)

ECOG, Eastern Cooperative Oncology Group; SD, standard deviation.

Figure 1. Proportion of Patients With TRAEs by Maximum Grade (Occurring in ≥ 20% of Patients; n = 34)



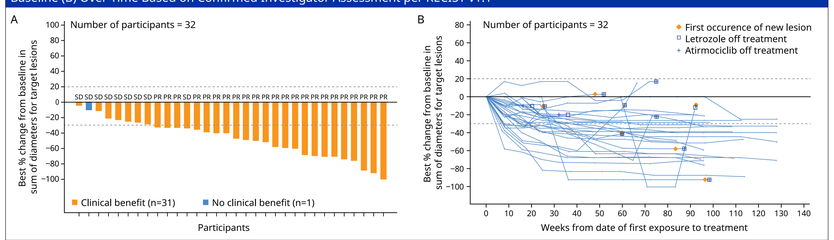
AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; TRAE, treatment-related adverse event.

Table 2. Confirmed Tumor Response Based on Investigator Assessment (RECIST v1.1)

Tumor Response	Cohort 2B
Best overall response, n (%)	**n = 34**
CR	0
PR	23 (67.6)
SD	9 (26.5)
PD	0
Non-CR/non-PD	1 (2.9)
Not evaluable	1 (2.9)
cORR, % (95% CI)	67.6 (49.5–82.6)
CBR, % (95% CI)	94.1 (80.3–99.3)
Patients with measurable disease at baseline	**n = 33**
cORR, % (95% CI)	69.7 (51.3–84.4)
CBR, % (95% CI)	93.9 (79.8–99.3)

95% CIs based on Clopper–Pearson method.
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 per RECIST v1.1. CBR, clinical benefit rate (CR + PR + non-CR/non-PD + ≥ 24 weeks SD); CI, confidence interval; cORR, confirmed objective response rate (CR + PR); CR, complete response; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Figure 2. Waterfall Plot of Best Percent Change From Baseline in Sum of Diameters of Target Lesions (A) and Spider Plot of Tumor Change From Baseline (B) 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.
PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

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