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Pharmacodynamic effects of the first-in-class CDK4-selective inhibitor atirmociclib (PF-07220060) in combination with endocrine therapy in tumors of patients with HR+/HER2– metastatic breast cancer

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Objectives

To evaluate pharmacodynamic effects, including CDK4 inhibition-related protein and gene expression profile changes in tumors of patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2–) metastatic breast cancer (mBC) treated with atirmociclib in combination with endocrine therapy (ET; fulvestrant) in the first-in-human clinical study.

Conclusions

Exploratory immunohistochemistry (IHC) and RNA-seq analyses of paired tumor biopsies from patients with HR+/HER2– mBC revealed the following pharmacodynamic effects of atirmociclib in combination with fulvestrant:

- Marked inhibition of cell cycle-related protein biomarkers and gene expression, including pRb, Ki67, and FOXM1, along with suppression of cell cycle-associated gene signatures, consistent with the mechanism of action (MOA) of atirmociclib as a CDK4 inhibitor (CDK4i).
- Increased tumor-associated macrophage fractions and upregulation of antigen presentation pathway genes, as determined by cell-type deconvolution of bulk RNA-sequencing (seq) data.
- Reprogramming of tumor intrinsic molecular subtypes, with a shift from more aggressive Luminal B and HER2-enriched subtypes to the less proliferative Luminal A subtype with improved prognosis.
- These results support the observed clinical activity and ongoing development of atirmociclib in HR+/HER2– mBC.

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Introduction

- Atirmociclib (PF-07220060) is a highly selective and potent CDK4i with sparing of CDK6.
- In an ongoing phase 1/2a trial (NCT04557449), atirmociclib plus ET demonstrated favorable safety, tolerability, and promising clinical activity in patients with HR+/HER2– mBC,[1,2] as well as potent pharmacodynamic effects on surrogate biomarkers, including inhibition of serum thymidine kinase activity and early decrease of circulating tumor DNA (ctDNA).[3,4]
- Here, we report results from further exploratory analyses of pharmacodynamic biomarkers and gene expression profiles in tumor biopsies from patients with HR+/HER2– mBC treated with atirmociclib in combination with fulvestrant, to demonstrate proof-of-mechanism and further elucidate the MOA of atirmociclib.

Materials and methods

STUDY DESIGN

- NCT04557449, an ongoing phase 1/2a, open label, multicenter, multiple-dose study, is evaluating the safety, tolerability, antitumor activity, and exploratory biomarkers of atirmociclib administered as a single agent and in combination with ET (letrozole or fulvestrant) or enzalutamide in patients with metastatic or advanced solid tumors.
- Patients with HR+/HER2– mBC were treated with atirmociclib (100, 300, or 400 mg twice daily) in combination with fulvestrant.
- Tumor response was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
- Fresh tumor biopsies were collected at baseline before the first dose (screening) and following one 28-day treatment cycle (cycle 2 day 1, C2D1).
- Plasma samples were collected at C1D1.

IHC ANALYSIS

- Formalin-fixed paraffin-embedded tumor biopsy samples were stained for expression of phospho-Rb (Ser807/811, pRb), Ki67, and FOXM1 by IHC.

ctDNA ANALYSIS

- Genomic alterations in ctDNA were determined using next-generation sequencing assays (Guardant360, or PredicineCARE for patients enrolled in China).

RNA-SEQUENCING AND GENE EXPRESSION ANALYSES

- Single-sample gene set variance analysis (GSVA) was performed on the log2(TPM) RNA-seq gene expression data using the R package GSVA (v.1.50.5).
- The Molecular Signatures Database Hallmark gene sets v.2023.2 were used to represent broad biological processes.
- An RB loss-of-function palbociclib resistance signature[5] and selected immune-related gene sets (PD1_signaling, antigen_processing_cross_presentation)[6] were also included. Cell-type deconvolution of the bulk RNA-seq data was performed using BayesPrism. For PAM50 subtyping, the R package genefu (v.2.34.0) was used to predict PAM50 subtypes from the log2(TPM) RNA-seq data.

Results

PATIENTS

- As of February 21, 2025, paired tumor biopsy samples were collected from 18 patients with HR+/HER2– mBC treated with atirmociclib plus fulvestrant (**Table 1**).
- Patients had received prior treatment with a CDK4/6i plus ET or ET alone.
- IHC (evaluable at least for 1 of pRb, Ki67, and FOXM1) and RNA-seq results were available in 14 and 14 patients, respectively.
- Alterations of key genes related to estrogen receptor and the CDK4/6i pathway and resistance detected in C1D1 ctDNA are shown in **Table 1**.
  - The most commonly mutated genes were *ESR1* and *PIK3CA*. RECIST responses were observed in tumors regardless of *ESR1* and *PIK3CA* mutation status, but not in tumors harboring *RB1* mutations.

IHC ANALYSIS

- Atirmociclib plus fulvestrant led to strong inhibition of pharmacodynamic biomarkers (pRb, Ki67, and FOXM1 by IHC) from baseline in C2D1 tumors (**Figure 1**).

RNA-SEQ and GENE EXPRESSION ANALYSES

- Atirmociclib plus fulvestrant led to downregulation of cell cycle-related pathway gene sets and upregulation of immune response pathway gene sets (**Figure 2**).
- Consistent with its MOA of cell cycle blockade, atirmociclib plus fulvestrant significantly downregulated gene expression in E2F, RB_LOF, G2M, mitotic, and MYC pathways, largely in tumors of patients who achieved a clinical benefit response (CBR). The treatment also led to upregulation of immune and inflammation response-related gene sets.
- Cell-type fraction estimation using BayesPrism bulk RNA-seq deconvolution revealed a decrease in tumor cell fraction and an increase in cancer-associated fibroblast fraction (**Figure 3A**). An increase in macrophage fraction was also observed, while no significant changes were detected in CD4$^+$ or CD8$^+$ T-cell fractions.
- Estimated macrophage fractions in tumor biopsies, collected at screening and C2D1, showed an increase in macrophage fractions in patients with a CBR (**Figure 3B**).
- **Figure 3C** shows a heat map revealing changes at C2D1 from baseline of gene expression in the antigen presentation pathway.
- Treatment with atirmociclib in combination with fulvestrant resulted in a shift of tumor intrinsic molecular subtypes, from more aggressive phenotypes to less proliferative subtypes associated with improved prognosis (**Figure 4**).
  - Among 13 tumors classified as Luminal B or HER2-enriched by PAM50 at baseline, 10 (77%) transitioned to the Luminal A subtype at C2D1.

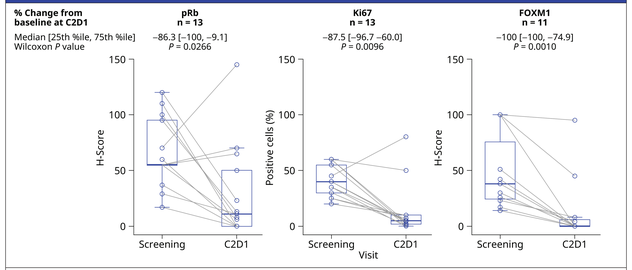
Table 1. Patient information and analysis summary of the biomarker cohort

Mutation / Amplification

Patient	Prior CDK4/6i	BOR	CBR	IHC	RNA-Seq	C1D1 ctDNA: *AKT1*	*CCND1*	*CDKN2A*	*ERBB2*	*ESR1*	*FGFR1*	*FGFR2*	*MYC*	*PIK3CA*	*PTEN*	*RB1*	*TP53*
1	N	PR	Y	Y	Y												
2	N	PR	Y	Y	Y												
3	N	PR	Y	N	Y												
4	N	PR	Y	N	Y												
5	N	PR	Y	Y	Y												
6	N	PR	Y	Y	Y												
7	N	PR	Y	Y	N												
8	N	PR	Y	Y	Y	ctDNA sample was not collected											
9	N	SD	Y	Y	Y												
10	N	SD	Y	Y	N												
11	**Y**	SD	Y	N	Y												
12	N	SD	Y	Y	Y												
13	**Y**	SD	Y	Y	Y												
14	N	SD	Y	Y	N												
15	**Y**	SD	N	Y	Y												
16	**Y**	PD	N	Y	N												
17	N	PD	N	Y	Y												
18	**Y**	PD	N	N	Y												

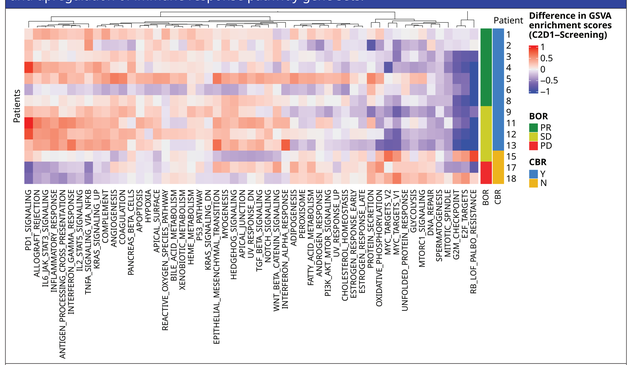
BOR, best overall response; C1D1, cycle 1 day 1; CBR, clinical benefit response; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ctDNA, circulating tumor DNA; IHC, immunohistochemistry; PD, progressive disease; PR, partial response; RNA-Seq, RNA-sequencing; SD, stable disease.

Figure 1. Atirmociclib plus fulvestrant led to strong inhibition of PD biomarkers (pRb, Ki67, and FOXM1 by IHC) in HR+/HER2– tumors



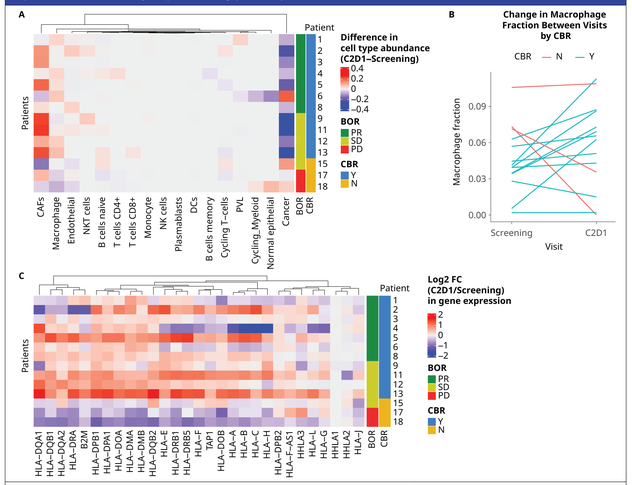
C2D1, cycle 2 day 1; HR+/HER2– hormone receptor-positive/human epidermal growth factor receptor 2-negative; IHC, immunohistochemistry; mBC, metastatic breast cancer; PD, pharmacodynamic.

Figure 2. Atirmociclib plus fulvestrant led to downregulation of cell cycle-related pathway gene sets and upregulation of immune response pathway gene sets.



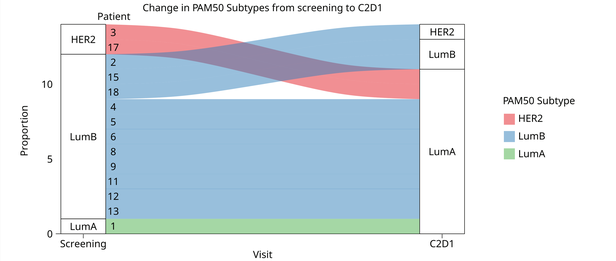
BOR, best overall response; C2D1, cycle 2 day 1; CBR, clinical benefit rate; GSVA, gene set variance analysis; PD, progressive disease; PR, partial response; pt, patient; SD, stable disease.

Figure 3. Atirmociclib plus fulvestrant led to decrease in the fraction of tumor cells and increase in the fractions of CAFs (A), an increase in macrophages in tumor biopsies (B), and changes in gene expression in the antigen presenting pathway (C).



BOR, best overall response; C2D1, cycle 2 day 1; CAF, cancer-associated fibroblast; CBR, clinical benefit response; DC, dendritic cell; PD, progressive disease; PR, partial response; PVL, perivascular-like cell; SD, stable disease.

Figure 4. Intrinsic molecular subtype switching following atirmociclib plus fulvestrant treatment



C2D1; cycle 2 day 1; HER2, human epidermal growth factor receptor 2; Lum, Luminal.

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