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Longitudinal circulating tumor DNA (ctDNA) dynamics in phase 1/2a study of the first-in-class CDK4-selective inhibitor, atirmociclib (PF-07220060), in combination with endocrine therapy in patients with HR+/HER2– metastatic breast cancer (mBC) who progressed on prior CDK4/6 inhibitors

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Objective

To conduct exploratory circulating tumor DNA (ctDNA) analyses in patients with HR+/HER2– metastatic breast cancer (mBC) treated with atirmociclib (PF-07220060) plus endocrine therapy (ET) enrolled in the dose escalation cohorts (Parts 1B/C) of the first-in-human atirmociclib trial.

Conclusions

- Atirmociclib plus ET led to a significant early decrease in ctDNA in patients with HR+/HER2– mBC. *ESR1* and *PIK3CA* mutant alleles in ctDNA were also markedly reduced.
- Patients with greater ctDNA reduction from baseline at cycle 1 day 15 (C1D15) were more likely to have favorable clinical outcomes.
- At end of treatment (EOT) when patients developed progressive disease, ctDNA increased to baseline levels. Emerging gene alterations in EOT ctDNA, such as *RB1* mutations, suggest potential resistance mechanisms to CDK4 inhibition by atirmociclib.
- These findings were from a small number of patients and will be further evaluated in Part 2 of this study.

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Introduction

- Atirmociclib is a novel potent CDK4-selective inhibitor with sparing of CDK6.
- In an ongoing phase 1/2a study (NCT04557449), atirmociclib combined with ET demonstrated a favorable safety profile and promising clinical activity in patients with HR+/HER2– mBC who progressed on a prior CDK4/6 inhibitor (CDK4/6i).[1,2]
- Baseline ctDNA level and its change following anticancer drug treatment can be of prognostic and predictive value.[3]
- Studies of patients with HR+/HER2– mBC treated with CDK4/6i in combination with ET showed an early decrease in ctDNA (i.e., molecular response [MR]), which could be both a pharmacodynamic biomarker and predictive of reduced risk of disease progression.[3,4]

Methods

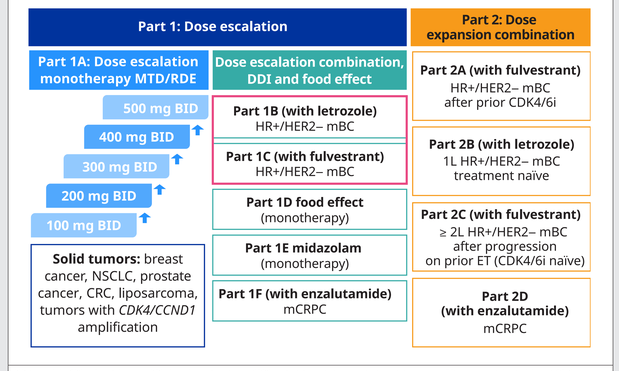
STUDY DESIGN

- This is an ongoing phase 1/2a (NCT04557449), open label, multicenter, multiple dose study evaluating the safety, tolerability, antitumor activity and exploratory biomarkers of atirmociclib administered as a single agent and in combination with ET or enzalutamide in patients with metastatic or advanced solid tumors (**Figure 1**).
- Patients with HR+/HER2– mBC who had received prior treatments, including ET and CDK4/6i, were enrolled in Parts 1B and 1C and received 300 mg or 400 mg atirmociclib combined with letrozole (1B) or fulvestrant (1C).
- Exploratory biomarkers analyses included tumor gene mutation profile at baseline and EOT, early dynamics of ctDNA response, and their relationship to clinical outcomes.

ctDNA ANALYSES

- Plasma samples were collected from patients at Cycle 1 Day 1 (C1D1), C1D15 and EOT.
- Genomic alterations in ctDNA were determined using next-generation sequencing (NGS)-based 74-gene Guardant360 platform (Guardant Health, Redwood City, CA, USA) that detects mutation (single nucleotide variant [SNV]), small insertion and deletion (indel), amplification and fusion.
- ctDNA MR between two sampling time points was determined as previously described.[5] Briefly, after filtering germline variants and potential CHIPs (clonal hematopoiesis of indeterminate potential), mean variant allele frequency (VAF) of somatic variants (including SNVs, indels and fusions) with mutant molecular count above a proprietary threshold was calculated for each sample by averaging the VAFs of all variants detected in both samples.
  - The relative change of mean VAF of the post-treatment sample from the baseline sample was then calculated as the ctDNA MR.
  - Samples lacking somatic variants with sufficient mutant molecular counts or absence of any somatic alterations at both time points were considered ctDNA Low and not evaluable for MR.

Figure 1. Overall study design (NCT04557449)



BID, twice daily; CRC, colorectal cancer; DDI, drug-drug interaction; mCRPC, metastatic castration resistant prostate cancer; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; RDE, recommended dose for expansion.

Results

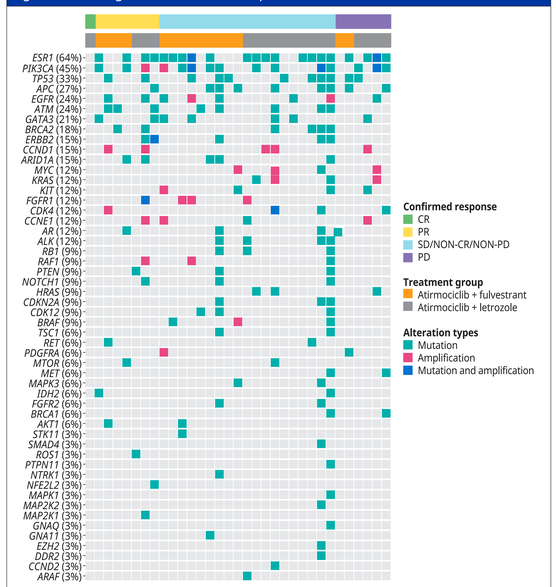
PATIENTS

- In Parts 1B and 1C, 33 patients received 300 or 400 mg BID atirmociclib + ET (letrozole [n = 18] or fulvestrant [n = 15]).
- Median age was 62.0 years (range, 41–82), all were female, 66.7% were White, 63.6% had an ECOG PS of 1 and the median of prior lines of systemic therapy in the metastatic setting was 4. All patients had prior CDK4/6i treatment.

BIOMARKER ANALYSES

- **Figure 2.** Tumor gene mutation landscape in C1D1 ctDNA (n = 33) was consistent with the mutation profile of HR+/HER2– mBC. The most frequently altered genes included *ESR1* (64%), *PIK3CA* (45%) and *TP53* (33%).
- **Figure 3.** Results of longitudinal ctDNA mean VAF change at C1D15 from C1D1 were available for 26 patients (14 in 1B, 12 in 1C; 6 were not included due to Low ctDNA and non-evaluable MR). Atirmociclib + ET led to significant early reduction of ctDNA at C1D15 in Parts 1B **(A)** and 1C **(B)**. Similar levels of early ctDNA decreases were observed in Parts 1B and 1C **(C)**.
- **Figure 4.** Significant decreases in the VAF of *ESR1* **(A)** and *PIK3CA* **(B)** were observed at C1D15 from C1D1 in patients with known mutations at baseline. There was a total of 44 *ESR1* variants in 21 patients and 20 *PIK3CA* variants in 13 patients.
- **Figure 5.** A plot of the best tumor size change vs ctDNA MR at C1D15 from baseline (n = 19) shows that a decrease of ≥ 50% in mean VAF was necessary for achieving ≥ 30% best tumor dimension reduction and RECIST v1.1 partial response **(A)**. Patients with Low ctDNA at C1D15 trended towards having longer progression-free survival than patients with High ctDNA **(B)**.
- **Figure 6.** ctDNA levels increased to baseline levels at EOT **(A)**; solid lines indicate longitudinal C1D15 and EOT MR results from the same patient. Alterations in cell cycle and CDK4/6i-related genes identified in C1D1 and EOT ctDNA of patients with paired samples may inform potential resistance mechanisms to atirmociclib **(B)**. *RB1* mutations were acquired in 3 of 16 patients at EOT, consistent with resistant mechanism to CDK4/6i. Selection for other gene alterations (e.g., *TP53, EGFR* and *CCNE1)* in EOT ctDNA was also observed (*).

Figure 2. Tumor gene mutation landscape in baseline ctDNA



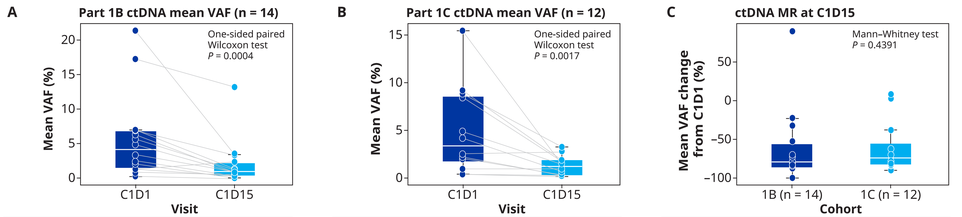
Guardant360 platform detects mutation, indel, fusion and amplification (including focal and non-focal amplifications) of 74 genes. Copy number loss is not reported. Patients are ordered based on confirmed best overall response per RECIST v1.1 criteria and treatment groups. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Table 1. Atirmociclib + ET demonstrated clinical activity irrespective of *ESR1* or *PI3K* pathway gene mutations in baseline ctDNA

	***ESR1* mutations**		***PIK3CA*, *ATK1* and *PTEN* mutations (one or more)**	
Parts 1B and 1C (n = 33)	**Yes (n = 21)**	**No (n = 12)**	**Yes (n = 15)**	**No (n = 18)**
Best overall response, n (%)				
Complete response (CR)	0	1 (8.3)	0	1 (5.6)
Partial response (PR)	4 (19.0)	3 (25.0)	4 (26.7)	3 (16.7)
Non-CR/Non-PD	4 (19.0)	1 (8.3)	3 (20.0)	2 (11.1)
Stable disease (SD)	9 (42.9)	5 (41.7)	5 (33.3)	9 (50.0)
Progressive disease (PD)	4 (19.0)	2 (16.7)	3 (20.0)	3 (16.7)
Objective response (CR + PR), n (%) [95% CI]	4 (19.0) [6.3–42.6]	4 (33.3) (11.3–64.6]	4 (26.7) [8.9–55.2]	4 (22.2) [7.4–48.1]
Clinical benefit response (CR + PR + SD for 24 weeks), n (%) [95% CI]	11 (52.4) [30.3–73.6]	9 (75.0) [42.8–93.3]	9 (60.0) [32.9–82.5]	11 (61.1) [36.1–81.7]

ESR1, *PIK3CA*, *AKT1* and *PTEN* variants include alterations defined in elacestrant, alpelisib and capivasertib companion diagnostic tests.
CI, confidence interval; ET, endocrine therapy.

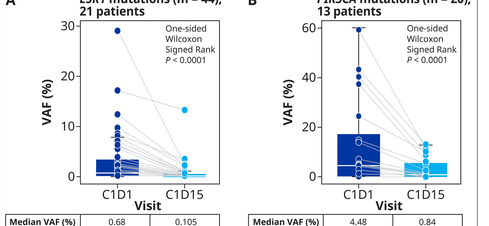
Figure 3. Atirmociclib + ET led to significant early reduction of ctDNA in patients with HR+/HER2– mBC



	A	B	C
Median VAF (%) [IQR]	4.09 [1.45, 6.68]	0.92 [0.39, 2.08]	
Median VAF (%) [IQR]	3.35 [1.78, 8.48]	1.22 [0.35, 1.86]	
Median MR C1D15/C1D1			–79.5% / –74.0%

C1D1, cycle 1 day 1; C1D15, cycle 1 day 15; ctDNA, circulating tumor DNA; ET, endocrine therapy; IQR, interquartile range; mBC, metastatic breast cancer; VAF, variant allele frequency.

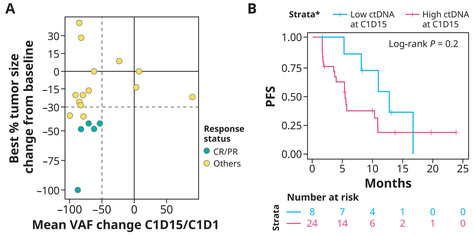
Figure 4. Atirmociclib + ET led to early decrease of *ESR1* and *PIK3CA* mutant alleles in ctDNA



	A	B
Median VAF (%) [IQR]	0.68 [0.16, 3.37]	0.105 [0, 0.47]
Median VAF (%) [IQR]	4.48 [0.22, 17.12]	0.84 [0, 5.53]

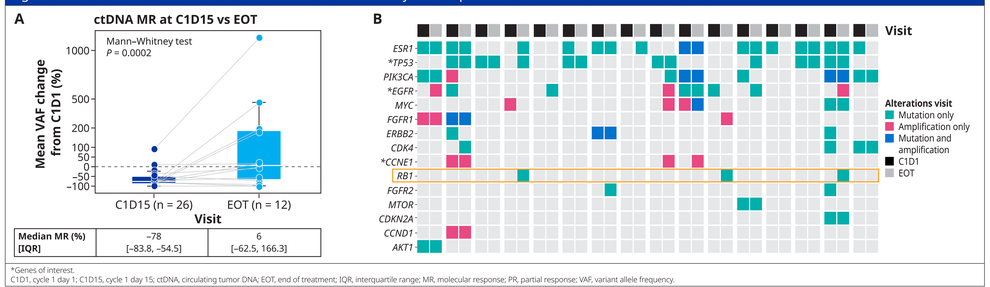
C1D1, cycle 1 day 1; C1D15, cycle 1 day 15; ctDNA, circulating tumor DNA; ET, endocrine therapy; IQR, interquartile range; VAF, variant allele frequency.

Figure 5. Patients with greater ctDNA reduction at C1D15 were more likely to achieve favorable clinical outcomes



*Low ctDNA: ctDNA undetectable or MR non-evaluable; High ctDNA: ctDNA MR evaluable.
C1D1, cycle 1 day 1; C1D15, cycle 1 day 15; CR, complete response; ctDNA, circulating tumor DNA; MR, molecular response; PFS, progression-free survival; PR, partial response; VAF, variant allele frequency.

Figure 6. ctDNA at EOT increased to the baseline levels and may inform potential resistance mechanisms to atirmociclib



	A	B
Median MR (%) [IQR]	–78 [–83.8, –54.5]	6 [–62.5, 166.3]

*Genes of interest.
C1D1, cycle 1 day 1; C1D15, cycle 1 day 15; ctDNA, circulating tumor DNA; EOT, end of treatment; IQR, interquartile range; MR, molecular response; PR, partial response; VAF, variant allele frequency.

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