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Effect of atirmociclib plus endocrine therapy (ET) on serum thymidine kinase activity (TKa) in a phase 1 study of patients with HR+/HER2– metastatic breast cancer (mBC)

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Objective

- To evaluate serum TKa and the relationship between changes in TKa and progression-free survival (PFS) in patients with hormone receptor-positive/human epidermal growth factor 2-negative (HR+/HER2–) mBC following treatment with atirmociclib (PF-07220060) in combination with ET in the first-in-human atirmociclib clinical study

Conclusions

- Treatment with atirmociclib in combination with ET yielded strong inhibition of serum TKa in patients with HR+/HER2– mBC, demonstrating pharmacodynamic (PD) target modulation effects
- Overall, lower baseline TKa was associated with longer PFS
- Patients with sustained complete inhibition of TKa at cycle (C) 1 day (D) 15 and C2D1 tended to have longer PFS, suggesting deeper CDK4 target modulation by atirmociclib may lead to improved clinical outcome

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References: 1. Yap et al. *J Clin Oncol*. 2023;41(suppl_16):3009. **2.** Giordano et al. Poster presentation at the San Antonio Breast Cancer Symposium, December 10-13, 2024, San Antonio, TX. Abstract #P5-07-28. **3.** Migliaccio et al. *Cancers (Basel)*. 2021;13:2640. **4.** Malorni et al. *Eur J Cancer*. 2023;186:1-11. **5.** McCartney et al. *Clin Cancer Res*. 2020;26:2131-2139. **6.** Xu et al. *Cancer Res*. 2018;78(suppl_13): Abstract #CT048.

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Introduction

- Atirmociclib is a highly selective and potent cyclin-dependent kinase (CDK) 4 inhibitor with sparing of CDK6[1]
- In an ongoing phase 1/2a study (NCT04557449), atirmociclib plus ET has demonstrated favorable safety, tolerability, clinical activity, and robust PD activities in patients with HR+/HER2– mBC[1,2]
- Thymidine kinase (TK1) is a Rb-E2F regulated target gene that plays an important role in DNA replication and the cell cycle[3]
- Serum TKa level and changes have been found to be associated with the clinical activity of CDK4/6 inhibitors[4,5]
- TKa can be assayed in serum and used as a PD biomarker of CDK4/6 inhibitor response in patients with HR+/HER2– mBC[3]

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
- Parts 1B and 1C enrolled patients with HR+/HER2– mBC who had received prior treatments, including ET and CDK4/6 inhibitors. These patients received atirmociclib (300 mg or 400 mg bid) in combination with letrozole (1B) or fulvestrant (1C)
- Part 2B enrolled patients with HR+/HER2– mBC who had not received any systemic therapy in the metastatic setting. These patients received first-line atirmociclib (300 mg bid) in combination with letrozole
- Exploratory biomarkers analyses included assessment of serum TKa and its changes following atirmociclib treatment, as well as the relationship with clinical outcomes

SERUM TKa ANALYSIS

- Serum samples were collected from enrolled patients at C1D1 (baseline), C1D15, and C2D1
- TKa was determined via the ELISA-based DiviTum assay (Biovica, Uppsala, Sweden) that measures bromo-deoxyuridine (BrdU) incorporation into an immobilized synthetic DNA strand, which is further detected using anti-BrdU monoclonal antibody
- The resulting signal in the sample was expressed as DiviTum unit of activity (DuA)
- Limit of quantitation (LoQ) of each batch sample analysis was determined using the 6-point calibration curve of the assay
- In data analyses, TKa levels below LoQ were imputed as 0.5 X LoQ

ASSOCIATION OF TKa WITH PFS

- PFS by cohorts and by subgroups were estimated with Kaplan–Meier curves; subgroups included baseline TKa (> 25th vs ≤ 25th percentile) and sustained complete TKa inhibition (yes vs no)
  - Sustained complete TKa inhibition was defined as having a value below LoQ at both C1D15 and C2D1
- A stratified Cox regression model was used to estimate the hazard ratio (HR) and confidence interval (CI) while accounting for the potential difference in baseline hazards across cohorts

Results

PATIENTS

- As of November 1, 2024, 33 patients were enrolled in Part 1B/1C and 34 patients in Part 2B
- In Part 1B/1C, patients had a median age of 62 years (range, 41–82). All patients were female and most were White (66.7%); 66.7% had ≥ 3 prior systemic lines of therapy in the advanced/metastatic setting (median: 4.0)
- In Part 2B, patients had a median age of 59 years (range: 32–84). All patients were female and most were White (67.6%); no patients had received any systemic therapy in the advanced/metastatic setting, as per protocol
- Serum TKa results were available for all patients in Part 1B/1C (n = 33) and 25 patients in Part 2B (biomarker analysis set); biomarker analyses were performed in these patients

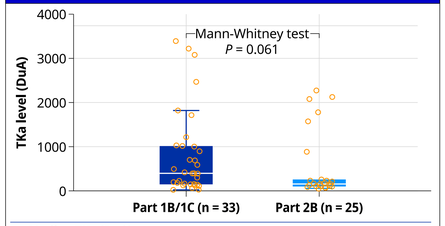
SERUM TKa ANALYSIS

- Baseline serum TKa levels were lower in patients in Part 2B compared with patients in Part 1B/1C, although the difference was not statistically significant (*P* = 0.061) (**Figure 1**)
- Atirmociclib in combination with letrozole or fulvestrant achieved continued strong inhibition of serum TKa at both C1D15 and C2D1 in patients in Part 1B/1C (**Figure 2A**) and Part 2B (**Figure 2B**), without the significant rebound observed for palbociclib at C2D1 after a one-week treatment break[6]

ASSOCIATION OF TKa WITH PFS

- Median PFS was 8.1 months (95% CI: 5.3–12.7) in Part 1B/1C (n = 33) and not reached in Part 2B (n = 25, biomarker analysis set)
- When patients were grouped by baseline TKa (n = 58), those with low baseline TKa (lower 25th percentile: ≤ 122.2 DuA) had longer PFS than patients with higher baseline TKa (HR = 0.15; 95% CI: 0.04–0.64)
- This effect was consistently observed in both Part 1B/1C and Part 2B, despite the cohorts having different baseline hazard rates (**Figure 3**)
- TKa levels by visits of patients grouped by sustained complete TKa inhibition (n = 20) and incomplete TKa inhibition (n = 38) are shown in **Figure 4A**
- Overall, patients with sustained complete TKa inhibition had more favorable PFS than those who had incomplete TKa inhibition (HR = 0.47; 95% CI: 0.20–1.09)
- This pattern was consistent across cohorts, despite the cohorts having different baseline hazard rates (**Figure 4B**)

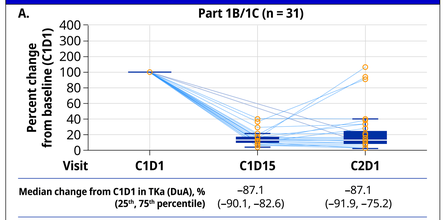
Figure 1. Baseline serum TKa levels



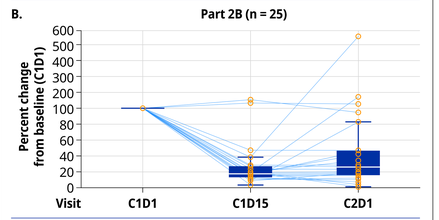
Median TKa (DuA) (25th, 75th percentile)	Part 1B/1C (n = 33)	Part 2B (n = 25)
	397.3 (152.0, 1015.0)	152.6 (102.2, 255.7)

DuA, DiviTum unit of activity; TKa, thymidine kinase activity.

Figure 2. Serum TKa change from baseline



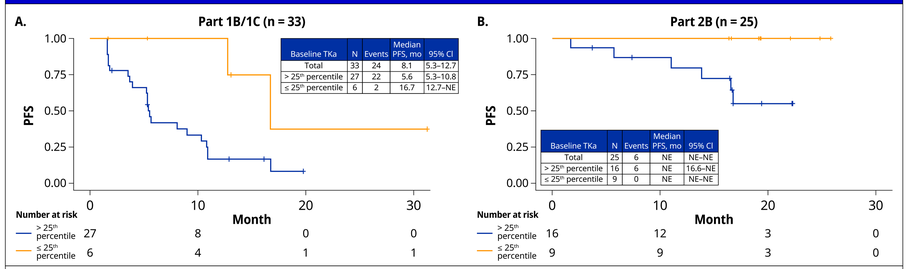
Median change from C1D1 in TKa (DuA), % (25th, 75th percentile)	C1D15	C2D1
	−87.1 (−90.1, −82.6)	−87.1 (−91.9, −75.2)



Median change from C1D1 in TKa (DuA), % (25th, 75th percentile)	C1D15	C2D1
	−82.3 (−86.7, −73.4)	−76.8 (−84.3, −53.5)

Two patients with TKa < LoQ at C1D1 were excluded from the analysis in Part 1B/1C.
C, cycle; D, day; DuA, DiviTum unit of activity; LoQ, limit of quantitation; TKa, thymidine kinase activity.

Figure 3. Association of baseline TKa with PFS

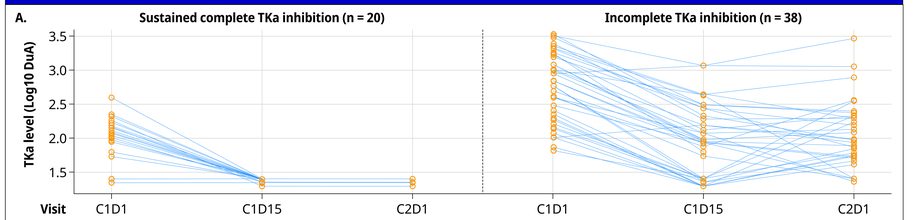


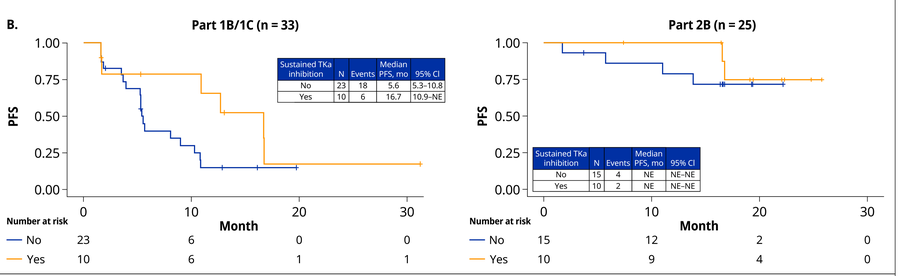
Baseline TKa	N	Events	Median PFS, mo	95% CI
Total	33	24	8.1	5.3–12.7
> 25th percentile	27	22	5.6	5.3–10.8
≤ 25th percentile	6	2	16.7	12.7–NE

Baseline TKa	N	Events	Median PFS, mo	95% CI
Total	25	6	NE	NE–NE
> 25th percentile	16	6	NE	16.6–NE
≤ 25th percentile	9	0	NE	NE–NE

CI, confidence interval; mo, month; NE, not estimable; PFS, progression-free survival; TKa, thymidine kinase activity.

Figure 4. TKa levels by inhibition groups (A) and relationship between TKa inhibition and PFS (B)





Sustained TKa inhibition	N	Events	Median PFS, mo	95% CI
No	23	18	5.6	5.3–10.8
Yes	10	6	16.7	10.9–NE

Sustained TKa inhibition	N	Events	Median PFS, mo	95% CI
No	15	4	NE	NE–NE
Yes	10	2	NE	NE–NE

Sustained complete TKa inhibition defined as below LoQ at both C1D15 and C2D1.
C, cycle; CI, confidence interval; D, day; LoQ, limit of quantitation; mo, month; NE, not estimable; PFS, progression-free survival; TKa, thymidine kinase activity.