

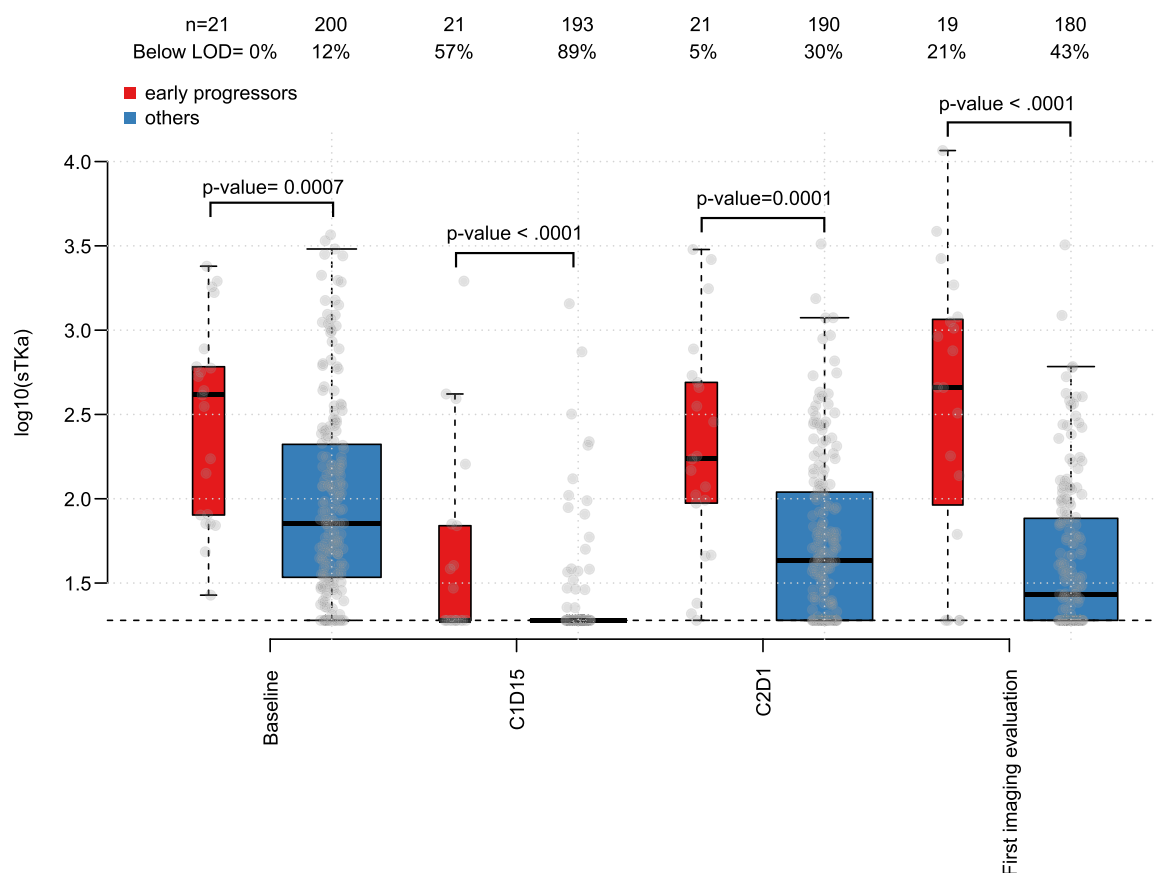


Fig. 4. sTKa levels over scheduled time points for early progressors versus other patients. Early progressors were patients who experienced disease progression within 112 days after treatment start. Dots represent individual data; dots outside upper and lower fences are considered outliers (higher or lower than $1.5 \times Q1-Q3$ range). sTKa levels recorded as < 20 Du/L have been considered as 19 Du/L to calculate median values. C, cycle; D, day; Du, DiviTum units; LOD, limit of detection; sTKa, serum thymidine kinase activity.

Pfizer, Roche, and Seagen; has received travel support from Roche; has participated in advisory board meetings for AstraZeneca, Daiichi Sankyo, Eli Lilly, MSD, Novartis, Pierre Fabre, Pfizer, Roche, and Seagen. M.C. has received a research grant from Roche and is co-chair of the IBCSG scientific committee. C.Z. has participated in advisory board meetings for Amgen, AstraZeneca, Celgene, Eisai, Lilly, Novartis, Pfizer, PharmaMar, QuintilesIMS, Roche, and Tesaro; has received honoraria from Istituto Gentili and Pierre Fabre; has received institutional research grants from AbbVie, Array BioPharma, AstraZeneca, Istituto Gentili, Medivation, Morphotek, Novartis, Pierre Fabre, Pfizer, Roche, Seattle Genetics, Synthon, Takeda, Tesaro, and TEVA. M.E.C. has received institutional consultancy fees from Eisai and Eli Lilly; has received honoraria from Eisai, Eli Lilly, Novartis, Pierre Fabre, Roche, and Seagen; has participated in advisory board meetings for Unicancer; is president of the scientific committee 'Qui donna si cura onlus.' M.O. has received travel support from Eisai and Roche; has participated in advisory board meetings for Amgen, AstraZeneca, Eisai, Eli

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Role of the funding source

The funding source was involved in the study design, the collection, analysis, and interpretation of data, and the writing of the manuscript.

Authors' contributions

L.M., G.B., G. Arpino, M.D.L.: Conceptualisation, Supervision; L.M., Writing – original draft; All authors: Data curation, Formal analysis, Writing – review & editing.

Data sharing statement

Novartis is committed to sharing with qualified external researchers, access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided is anonymised to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. This trial data availability is according to the criteria and process described on www.clinicalstudydatarequest.com.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.ejca.2023.03.001](https://doi.org/10.1016/j.ejca.2023.03.001).

References

- [1] McCartney A, Migliaccio I, Bonechi M, et al. Mechanisms of resistance to CDK4/6 inhibitors: potential implications and biomarkers for clinical practice. *Front Oncol* 2019;9:666.
- [2] Hui R, de Boer R, Lim E, et al. CDK4/6 inhibitor plus endocrine therapy for hormone receptor-positive, HER2-negative metastatic breast cancer: the new standard of care. *Asia Pac J Clin Oncol* 2021;17(Suppl. 1):3–14.
- [3] Migliaccio I, Bonechi M, McCartney A, et al. CDK4/6 inhibitors: a focus on biomarkers of response and post-treatment therapeutic strategies in hormone receptor-positive HER2-negative breast cancer. *Cancer Treat Rev* 2021;93:102136.
- [4] Bagegni N, Thomas S, Liu N, et al. Serum thymidine kinase 1 activity as a pharmacodynamic marker of cyclin-dependent kinase 4/6 inhibition in patients with early-stage breast cancer receiving neoadjuvant palbociclib. *Breast Cancer Res* 2017;19(1):123.
- [5] McCartney A, Malorni L. Thymidine kinase-1 as a biomarker in breast cancer: estimating prognosis and early recognition of treatment resistance. *Biomark Med* 2020;14(7):495–8.
- [6] Krishnamurthy J, Luo J, Suresh R, et al. A phase II trial of an alternative schedule of palbociclib and embedded serum TK1 analysis. *NPJ Breast Cancer* 2022;8(1):35.
- [7] Cabel L, Rosenblum D, Lerebours F, et al. Plasma thymidine kinase 1 activity and outcome of ER+ HER2- metastatic breast cancer patients treated with palbociclib and endocrine therapy. *Breast Cancer Res* 2020;22(1):98.
- [8] Malorni L, Tyekucheva S, Hilbers FS, et al. Serum thymidine kinase activity in patients with hormone receptor-positive and HER2-negative metastatic breast cancer treated with palbociclib and fulvestrant. *Eur J Cancer* 2022;164:39–51.
- [9] Arpino G, Bianchini G, Malorni L, et al. Circulating tumor DNA (ctDNA) and serum thymidine kinase 1 activity (TKa) matched dynamics in patients (pts) with hormone receptor-positive (HR+), human epidermal growth factor 2-negative (HER2-) advanced breast cancer (ABC) treated in first-line (1L) with ribociclib (RIB) and letrozole (LET) in the BioItaLEE trial. *J Clin Oncol* 2022;40(Suppl. 16): 1012–1012.
- [10] McCartney A, Bonechi M, De Luca F, et al. Plasma thymidine kinase activity as a biomarker in patients with luminal metastatic breast cancer treated with palbociclib within the TReND trial. *Clin Cancer Res* 2020;26(9):2131–9.
- [11] Paoletti C, Barlow WE, Cobain EF, et al. Evaluating serum thymidine kinase 1 in patients with hormone receptor-positive metastatic breast cancer receiving first-line endocrine therapy in the SWOG S0226 trial. *Clin Cancer Res* 2021;27(22):6115–23.
- [12] Bianchini G, Pusztai L, Karn T, et al. Proliferation and estrogen signaling can distinguish patients at risk for early versus late relapse among estrogen receptor positive breast cancers. *Breast Cancer Res* 2013;15(5):R86.