Editorial

Abemaciclib-based therapy versus tucidinostat-based therapy in patients with HR$^+$HER2$^-$ metastatic breast cancer after palbociclib progression: insights and challenges from a comparative cohort study in China

Nino Balanchivadze[1], Nicholas J. Robert[2]

[1]Virginia Oncology Associates/US Oncology Network, Norfolk, VA, USA; [2]Ontada, Boston, MA, USA

Correspondence to: Nicholas J. Robert, MD. Ontada, 33 Arch Street, 20th Floor, Boston, MA 02109, USA. Email: nicholas.robertmd@mckesson.com.

Comment on: Yuan Y, Zhang S, Wang T, *et al.* Efficacy and safety of abemaciclib-based therapy versus tucidinostat-based therapy after progression on palbociclib in patients with HR$^+$HER2$^-$ metastatic breast cancer. Transl Breast Cancer Res 2023;4:10.

Keywords: Hormone receptor-positive human epidermal growth factor receptor-2-negative metastatic breast cancer (HR$^+$HER2$^-$ MBC); abemaciclib; tucidinostat; personalized medicine

Received: 01 September 2023; Accepted: 11 October 2023; Published online: 23 October 2023.

doi: 10.21037/tbcr-23-45

View this article at: https://dx.doi.org/10.21037/tbcr-23-45

The landscape of hormone receptor-positive human epidermal growth factor receptor-2 (HER2)-negative metastatic breast cancer (HR$^+$HER2$^-$ MBC) has seen remarkable advancements in recent years. First-line therapy for HR$^+$HER2$^-$ MBC involves the standard combination of cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) with endocrine treatment (ET), as recommended by all major guidelines (1-3). This approach has demonstrated significant benefits in improving patient outcomes (4-6). However, the eventual progression on CDK4/6i necessitates the exploration of alternative treatment strategies to effectively combat disease progression and prolong survival.

Efforts have been directed towards understanding resistance mechanisms and reducing treatment toxicity, with a focus on extending the time to cytotoxic chemotherapy to enhance patients' quality of life and overall survival. Beyond first-line therapy, oncologists often face the challenge of sequencing therapies for patients with HR$^+$HER2$^-$ MBC, striving to identify the most suitable approach for patients. Attempts to establish the efficacy of CDK4/6i beyond progression on prior CDK4/6 inhibition have yielded varied outcomes. The MAINTAIN trial demonstrated a significant progression-free survival (PFS) benefit for patients with HR$^+$/HER2$^-$ MBC who switched ET and received ribociclib compared with placebo after previous CDK4/6i. In contrast, the PACE trial revealed no evident PFS advantage, whereas the PALMIRA trial illustrated that maintaining a regimen of palbociclib alongside endocrine therapy did not yield superior PFS outcomes compared to endocrine therapy alone (7-9).

The emergence of tucidinostat, an oral subtype-selective histone deacetylase inhibitor, has offered a potential treatment option for patients with HR$^+$HER2$^-$ MBC in China. The approval of tucidinostat, in combination with exemestane, was based on the positive results of the ACE trial, where it demonstrated efficacy by improving PFS in patients who had progressed after prior endocrine therapy (10).

A second course of CDK4/6i or tucidinostat-based therapy is becoming a common practice in China. These options have been recommended as viable treatment strategies post-CDK4/6i, according to the guidelines of the Chinese Society of Clinical Oncology Breast Cancer (CSCO BC) (3).

To shed light on the efficacy and safety of abemaciclib-based therapy versus tucidinostat-based therapy after disease progression on palbociclib, Dr. Yuan and colleagues conducted a retrospective comparative cohort study. The study, conducted in collaboration with multiple Chinese research centers and utilizing data from the CSCO BC database, aimed to compare outcomes for patients with

HR^+HER2^- MBC receiving these therapies (11).

The results of the study, which included 149 patients, revealed significant differences between the outcomes seen in the two treatment groups. The abemaciclib group showed an improved clinical benefit rate (CBR) and prolonged PFS compared to the tucidinostat group. Furthermore, abemaciclib demonstrated consistent superiority in improving PFS compared to tucidinostat across various subgroups of patients. Moreover, patients with certain refractory factors, such as those with visceral disease, multiple sites of metastases, and several prior lines of endocrine therapy, derived substantial benefits from abemaciclib treatment. Additionally, the response to abemaciclib was not significantly influenced by prior response to palbociclib-based therapy. The unique properties of abemaciclib, including increased selectivity for CDK4 over CDK6 and continuous administration, may account for its superior clinical performance. The effectiveness of abemaciclib as a single agent may suggest that its activity is not exclusively reliant on endocrine pathways, possibly making it a viable option even in cases of endocrine resistance (12,13).

The study delved into the impact of genomic mutations, particularly PIK3CA and ESR1, on treatment outcomes. Their presence was associated with worse clinical outcomes in both abemaciclib and tucidinostat groups. Interestingly, only 43 out of 149 patients in the study underwent tumor testing for multigene sequencing. There is a need to increase awareness about the importance of metastatic tumor biopsies and genomic sequencing in patients who develop metastatic disease progression to gain valuable insights into individual patients' tumors and identify resistance mutations that may diminish the benefits of CDK4/6 inhibition.

Given the retrospective nature of these observations and the heterogeneity of the patient population, caution should be exercised regarding any conclusions. Differences in baseline patient characteristics between the abemaciclib and tucidinostat groups may partially explain the contrasting outcomes. The proportion of patients whose tumors did not respond to prior palbociclib therapy was slightly higher in the tucidinostat group, potentially contributing to the observed rapid disease progression. Additionally, there was a higher use of fulvestrant in the abemaciclib group compared to the tucidinostat group.

In addition, measuring response and progression outside of a clinical trial is usually not done in a uniform fashion, which can contribute to different clinical outcomes. Even if RECIST criteria are used, doing this retrospectively poses challenges.

Choosing the optimal treatment post-progression on initial CDK4/6i plus ET requires a nuanced evaluation, with somatic and germline mutational status playing a crucial role in guiding targeted therapy decisions. Encouraging clinical trial participation when discussing subsequent lines of therapy with patients is essential. For PIK3CA mutations, fulvestrant plus alpelisib is an option. Pending regulatory approval, capivasertib, supported by CAPITELLO-291 study data (14), is a viable second-line choice. For patients with a germline BRCA mutation, a PARP inhibitor (olaparib or talazoparib) is recommended. Elacestrant is a consideration for ESR1-mutant disease, particularly in those patients with ≥12 months of benefit from prior CDK4/6i. Fulvestrant plus everolimus is also an available option in the absence of somatic alterations, albeit with limited post-progression data on CDK4/6i. In cases of exhausted non-chemotherapy options or rapid progression, single-agent chemotherapy, and antibody-drug conjugates like trastuzumab deruxtecan or sacituzumab govitecan should be considered.

In conclusion, the comparative study between abemaciclib-based therapy and tucidinostat-based therapy offers insights for deciding on treatment strategies in patients with HR^+HER2^- MBC. However, these findings highlight the need for further research and prospective trials to guide evidence-based clinical decision-making.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Breast Cancer Research*. The article has undergone external peer review.

Peer Review File: Available at https://tbcr.amegroups.org/article/view/10.21037/tbcr-23-45/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://tbcr.amegroups.org/article/view/10.21037/tbcr-23-45/coif). NB has served on the advisory board for Gilead. NJR is a full-time employee for Ontada. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. NCCN Clinical Practice Guidelines in Oncology—Breast Cancer Version 4.2023. Accessed August 31, 2023. Available online: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
2. Cardoso F, Paluch-Shimon S, Senkus E, et al. ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020;31:1623-49.
3. Jiang Z, Li J, Chen J, et al. Chinese Society of Clinical Oncology (CSCO) Breast Cancer Guidelines 2022. Transl Breast Cancer Res 2022;3:13.
4. Finn RS, Martin M, Rugo HS, et al. Palbociclib and Letrozole in Advanced Breast Cancer. N Engl J Med 2016;375:1925-36.
5. Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. N Engl J Med 2016;375:1738-48.
6. Goetz MP, Toi M, Campone M, et al. MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer. J Clin Oncol 2017;35:3638-46.
7. Kalinsky K, Accordino MK, Chiuzan C, et al. Randomized Phase II Trial of Endocrine Therapy With or Without Ribociclib After Progression on Cyclin-Dependent Kinase 4/6 Inhibition in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer: MAINTAIN Trial. J Clin Oncol 2023;41:4004-13.
8. Mayer EL, Ren Y, Wagle N, et al. Palbociclib after CDK4/6i and endocrine therapy (PACE): a randomized phase II study of fulvestrant, palbociclib, and avelumab for endocrine pre-treated ER+/HER2– metastatic breast cancer. Cancer Res 2023;83:GS3-06.
9. Llombart-Cussac A, Harper-Wynne C, Perello A, et al. Second-line endocrine therapy (ET) with or without palbociclib (P) maintenance in patients (pts) with hormone receptor-positive (HR[+])/human epidermal growth factor receptor 2-negative (HER2[-]) advanced breast cancer (ABC): PALMIRA trial. J Clin Oncol 2023;41:1001.
10. Jiang Z, Li W, Hu X, et al. Tucidinostat plus exemestane for postmenopausal patients with advanced, hormone receptor-positive breast cancer (ACE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2019;20:806-15.
11. Yuan Y, Zhang S, Wang T, et al. Efficacy and safety of abemaciclib-based therapy versus tucidinostat-based therapy after progression on palbociclib in patients with HR+HER2– metastatic breast cancer. Transl Breast Cancer Res 2023;4:10.
12. Dickler MN, Tolaney SM, Rugo HS, et al. MONARCH 1, A Phase II Study of Abemaciclib, a CDK4 and CDK6 Inhibitor, as a Single Agent, in Patients with Refractory HR(+)/HER2(-) Metastatic Breast Cancer. Clin Cancer Res 2017;23:5218-24.
13. Wander SA, O'Brien N, Litchfield LM, et al. Targeting CDK4 and 6 in Cancer Therapy: Emerging Preclinical Insights Related to Abemaciclib. Oncologist 2022;27:811-21.
14. Turner NC, Oliveira M, Howell SJ, et al. Capivasertib in Hormone Receptor-Positive Advanced Breast Cancer. N Engl J Med 2023;388:2058-70.

doi: 10.21037/tbcr-23-45

Cite this article as: Balanchivadze N, Robert NJ. Abemaciclib-based therapy versus tucidinostat-based therapy in patients with $HR^{+}HER2^{-}$ metastatic breast cancer after palbociclib progression: insights and challenges from a comparative cohort study in China. Transl Breast Cancer Res 2023;4:32.

