Peer Review File

Article information: https://dx.doi.org/10.21037/tbcr-23-31

Reviewer Comments

Reviewer A

Comment 1: Well-written update of ACE trial with now safety and overall survival data.

Between July 20, 2015, and June 26, 2017, 365 patients were enrolled and randomly assigned, 244 to the tucidinostat group and 121 to the placebo group. Four years ago at a medium follow-up of 13·9 months (IQR 9·8-17·5) the median progression-free survival was 7·4 months (95% CI 5·5-9·2) in the tucidinostat group and 3·8 months (3·7-5·5) in the placebo group (HR 0·75 [95% CI 0·58-0·98]; p=0·033). The most common grade 3 or 4 adverse events in either group were neutropenia (124 [51%] of 244 patients in the tucidinostat group vs three [2%] of 121 patients in the placebo group), thrombocytopenia (67 [27%] vs three [2%]), and leucopenia (46 [19%] vs three [2%]). Serious adverse events of any cause occurred in 51 (21%) of 244 patients in the tucidinostat group and seven (6%) of 121 patients in the placebo group. No treatment-related deaths were reported.

In this analysis they have updated results following 26.5 months of follow-up with no differences in overall survival although the study was underpowered for this secondary endpoint.

Reply 1: Thanks for your kind comment.

Comment 2: Median treatment duration in both groups does compare very well with median PFS as reported in Lancet Oncology 2019 by the same authors. However, in the tucidinostat arm, patients were on therapy for a median duration of 24 weeks, while the median PFS was 7.4 months, which is much longer. Question: How many patients stopped the combination prior to progression?

Reply 2: Thanks for your comment. the median duration of cancer therapy was 24 weeks while some of the patients withdrew their therapy without disease progression. That's why the median PFS was 7.4 months, longer than 24 weeks. As shown in Table, there were 28 patients stopped the combination prior to progression

Reviewer B

Comment 1: First, the title needs to indicate the RCT research design of this study. Second, the abstract needs some revisions. The background did not indicate the importance of long-term outcomes of tucidinostat plus exemestane. The methods need to describe the duration of the treatment, measures of safety outcomes, and how the two groups of patients were followed up. The results need to describe the baseline clinical characteristics of the two groups, and the completion of the follow up of the two groups of patients. Details data and statistics for the safety outcomes of the two groups need to be presented. The conclusion needs comments for the clinical implications of the findings. Third, in the introduction of the main text, the authors did not explain why the

ACE trails did not report the findings on the long-term outcomes and why the long-term outcomes are important. Fourth, in the methodology of the main text, please describe the details of follow up. In statistics, please describe the handling of missing data, statistical software used, and P value for statistical significance. Finally, please consider to review and cite some potentially important papers: 1. Li J, Shui Z, Ouyang Q. Significant response to the combination of pyrotinib and letrozole in a patient with metastatic HER2-positive and hormone receptor-positive breast cancer: a case report. Ann Palliat Med 2021;10(9):10124-10129. doi: 10.21037/apm-21-2522. 2. Zhang HQ, Zhou JM, Zhang SH, Bian L, Xiao JY, Hao XP, Jiang ZF, Wang T. Efficacy and safety of low-dose everolimus combined with endocrine drugs for patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer. Ann Transl Med 2021;9(19):1493. doi: 10.21037/atm-21-4273. 3. Dai Q, Wang Y, Liao M, Chen H. Efficacy and safety of CDK4/6 inhibitors combined with endocrine therapy versus endocrine therapy alone in hormone receptor-positive, HER2-negative, advanced breast cancer: a systematic review and meta-analysis. Ann Palliat Med 2022;11(12):3727-3742. doi: 10.21037/apm-22-1306.

Reply 1: Thanks for your kind comment. we have revised the title and abstract part as you recommended. We have also add the reference you advised.