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Letter to Editor

# Zoledronic-acid plus neoadjuvant therapy is associated with provoking outcomes in Her2-positive breast cancer

*Keywords:*
Her2-positive breast cancer
Zoledronic acid
Pathological complete response rate

*Dear Editor,*

We recently came across Mei Liu et al meta-analysis, a comprehensive study published in 2023, and wish to discuss a few aspects.[1]

Firstly, we partially agree with the authors that Zoledronic Acid (ZA) did not improve the pathological complete response (pCR) rate. We caution generalization, especially for the human epidermal growth factor receptor 2 (Her2) negative breast cancer (BC), a limited population included in the studies selected for this metanalysis, and it is known to behave distinctly both biologically and clinically.

In the past few years, we have made significant strides in providing clinical evidence of ZA in the neoadjuvant setting for Her2-positive BC. In 2019, the first publication of the Zo-Nan-Tax trial, a single arm, phase 2 clinical study, which evaluated eight cycles of ZA in the neoadjuvant setting during an anthracycline, taxane and trastuzumab-containing regimen for women with operable BC. The study met its primary endpoint, reporting an overall pCR rate of 42 %. Moreover, the pCR rate in HR-positive patients was equivalent to HR-negative, respectively 40 % and 44 %.[2]

Secondly, the Mei Liu et al report that in a subpopulation of 545 patients, a higher mortality of the ZA group 56/270 compared to the control group 38/275 (HR = 1.48, 95 % CI 1.04–2.10, p = 0.03). This finding, which was not expected, suggests that patients with premenopausal status might have a worse prognosis if exposed to ZA based on unplanned analysis from previous adjuvant clinical trials. It is important to note that this finding requires further investigation and should not discourage using ZA in the neoadjuvant setting without carefully considering the patient's individual characteristics and risk factors.[1]

There is a recommendation from ASCO in offering adjuvant bone-modifying agents regardless of HR or Her2 status.[3] Data from a large meta-analysis of studies evaluating adjuvant ZA versus control accounting in early BC, demonstrated an improvement in several outcomes, including BC mortality, distance, and bone recurrence.[4] The clinical trials included in this meta-analysis were sufficiently powered to test survival differences, contrastingly with the Mei Liu et al study.[1] We also could not find a biological rationale to explain why pre-menopausal patients would have a worse prognosis by receiving ZA in the neoadjuvant setting. Still, it is reassuring that no survival detriment was reported in the large adjuvant trials.[4]

Moreover, given the limited number, we assumed that the authors did not discuss survival impacts on the Her2-positive population. We wish to provide survival data for the Her2 positive population once the Zonantax trial 5-year survival has just been reported. The recurrence-free and overall survival rates were respectively 79.3 % and 86.2 %, comparable to pivotal studies that used dual anti-Her2 blockage.[5]

To conclude, ZA demonstrated robust survival benefits in the adjuvant and tolerable safety in the neoadjuvant setting, underscoring the need for its use earlier in the patient's treatment journey, irrespective of the BC subtype.

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## Declaration of conflicts of interest

The authors declare no conflict of interest.

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