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Early Local Therapy for the Primary Site in De Novo Stage IV Breast Cancer: Results of a Randomized Clinical Trial (EA2108)

TO THE EDITOR:

Khan et al[1] have recently reported on the results of the EA2108 trial. Resection of the primary tumor with systemic therapy is controversial in patients with metastatic breast cancer. This trial will greatly contribute to clarifying this controversial issue by randomly assigned patients who have achieved systemic control with treatment. However, we have a few concerns regarding the interpretation of the study results.

First, as stated by the authors,[1] the hypothesis that mesenchymal stem cells in the primary disease form the basis of the metastasis pathophysiology is defended. Therefore, it is hypothesized that removing mesenchymal stem cells will reduce distant metastases rates.[2] On the other hand, it has been shown in animal models that surgery can induce metastasis by causing stress and increasing growth factor release.[3] Therefore, the effect of local treatments on locoregional relapses and overall survival (OS) has been questioned in advanced disease. However, distant metastasis status and the progression-free survival durations of the surgical and nonsurgical patient groups were not explained. In addition, in the first phase III study on this subject published by Badwe et al,[4] it was found that patients whose primary tumor was resected had a significantly shorter distant metastasis-free survival ($P = .012$). Thus, it was believed that the OS could not be prolonged even if the locoregional control was achieved by surgery. Revealing progression-free survival durations in the EA2108 study might answer many questions on this subject.

Compared with other studies (Tata Memorial Center study, the ABCSG-28 POSYTIVE Study, and the MF07-01 Study) on this issue, the most important advantage of the current study is that patients are treated with systemic chemotherapy before random assignment.[4-6] However, patients received systemic therapy for 4 to 8 months, and patients with at least stable disease were randomly assigned to surgery/systemic therapy arms. It is known from previous studies that patients with a good response to neoadjuvant therapy, especially those with a complete pathological response, have better survival.[7] In the surgery arm, the patients who achieved partial response to chemotherapy might have better OS compared with patients who had stable response to chemotherapy. In the current study, subgroup analyses according to the systemic treatment responses of the patients before the locoregional treatment were not reported. Therefore, locoregional therapy may improve OS only in patients with a complete or partial response. Hence, subgroup analyses on the basis of treatment response may explain these controversial issues and provide a strong basis for future studies.

In conclusion, the EA2108 study showed promising outcomes on primary tumor surgery in managing metastatic breast cancer, which is highly controversial in current oncology practice. In addition, the presentation and interpretation of the subgroup results will shed light on oncology practice.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.22.00404.

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DOI: https://doi.org/10.1200/JCO.22.00404; Published at ascopubs.org/journal/jco on July 12, 2022.

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