correspondence

Locoregional Therapy for Intact Primary Tumor in De Novo Stage IV Breast Cancer

TO THE EDITOR:

Khan et al[1] have recently reported on the results of the EA2108 trial. We congratulate the authors; however, we have some questions and concerns about the study's design, patient selection criteria, and results.

First, we have concerns about protocol violations on the basis of the inclusion criterion "Patients must be judged to be candidates for complete resection with free margins followed by radiation therapy [RT] (if radiation therapy is indicated)" (Protocol).[1] In the E2108 paper, 14.4% patients randomly assigned to early location therapy (ELT) did not receive primary breast surgery and 7.2% had no axillary surgery at all, and 8.4% had positive margins in the final pathology. In addition, adjuvant RT, which is inevitable after breast conserving surgery (BCS), was not applied in 12.9% of the patients. As Khan[2] emphasized previously, surgical margin positivity is considered an unacceptable vulnerability in terms of oncological safety. The ELT group should have fulfilled the oncological safety principals, namely, surgical margin negativity, lymph node evaluation, and obligation for the addition of RT for those treated with BCS. Otherwise, the rest of the local therapeutic approaches would be palliative.

On the other hand, of the patients randomly assigned to continued systemic therapy (CST), 18.8% (n = 22) had mastectomies or BCS. The authors emphasized that surgery and RT applications in the CST group were for *palliative* as in similar previous studies. However, sentinel lymph node biopsy/axillary lymph node dissection were applied together in 77% of the patients (17 of 22) who were randomly assigned to the CST group, and RT was also applied to 45% of patients (10 of 22) who underwent surgery. The role of these practices in palliation is doubtful and suggests the expectation of contribution to treatment. None of the published similar RCTs include any additional axillary interventions to palliative surgery in the nonoperative arm.[3-5] The curative intent of surgery and RT in the CST arm may statistically mask the cumulative effect of locoregional therapy (LRT) on overall survival (OS).

The treatment received sample analysis in the practice changing ACOSOG Z0011 study and modified intent-to-treat analysis excludes patients who do not receive the assigned treatment at the time of random assignment.[6-8] If the authors would provide us with an analysis that excluded patients who had no breast surgery at all, patients who had margin positivity, and patients who did not receive RT after BCS during random assignment in the ELT group, that treatment received sample or modified intent to treat analysis would be very informative for the readers.

Aspects of the methodology used in the E2108 study were also interesting. Patients with a history of invasive breast malignancy ≥ 5 years previously were included. We believe that the literature on genuine dn stage IV BC has been well established; this stage is defined as parallel progression, not linear, slow growth from a neglected primary tumor or with a history of BC. In addition, E2108 included only 16% of oligometastatic patients, the vast majority of whom had multiple organ metastasis (84%). As such, the study could not reflect the data from the group that was most expected to respond to LRT.

Studies show that OS and progression-free survival rates were 98% and 100% in 10 years, respectively, in patients with human epidermal growth factor receptor 2–positive dn stage IV BC when they reach no evidence of disease.[9] In the E2108 study, 9% of patients had no evidence of disease (metastasis); we would like to ask the authors what their approach would be in such cases.

Unfortunately, for an unclear reason, the E2108 authors cited only the MF 07-01 abstract. LRT does not contribute to 3-year survival in the early period similar to the E2108 study; however, the long-term results of the MF 07-01 study in the peer-reviewed publication, which was not cited by Khan et al, showed that local control provides a significant survival advantage in all subgroups except for the patients with TN BC in both 5-year and 10-year OS (hazard ratio, 0.66, $P = .005$ and hazard ratio, 0.71, $P = .0003$, respectively).[5,10]

In light of this discussion, we think it is incorrect to suggest that LRT does not provide a survival advantage in dn stage IV BC on the basis of the results of a study with a limited follow-up. Systemic therapy has improved substantially, and patients live longer; long-term results of E2108 on LRT should be analyzed. Jumping to an early conclusion regarding survival with a limited follow-up period is premature.

Atilla Soran, MD, MPH, FNCBC
University of Pittsburgh Magee-Womens Hospital, Pittsburgh, PA

Ozgur Aytac, MD, FEBS
Baskent University, Adana, Turkey

Serdar Ozbas, MD, FEBS
Private Practice, Ankara, Turkey

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.22.00802.

ACKNOWLEDGMENT

Written on behalf of the Breast Health Working Group International.

REFERENCES

1. Khan SA, Zhao F, Goldstein LJ, et al: Early local therapy for the primary site in de novo stage IV breast cancer: Results of a randomized clinical trial (EA2108). J Clin Oncol 40:978-987, 2022
2. Khan SA: Does resection of an intact breast primary improve survival in metastatic breast cancer? Oncology 21:924-924, 2007
3. Badwe R, Hawaldar R, Nair N, et al: Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: An open-label randomised controlled trial. Lancet Oncol 16:1380-1388, 2015
4. Fitzal F, Balic M, Bjelic-Radisic V, et al: Primary operation in synchroneous metastasized invasive breast cancer patients: First oncologic outcomes of the prospective randomized phase III ABCSG 28 POSYTIVE trial. J Clin Oncol 35, 2017 (suppl 15; abstr 557)
5. Soran A, Ozmen V, Ozbas S, et al: Randomized trial comparing resection of primary tumor with no surgery in stage IV breast cancer at presentation: Protocol MF07-01. Ann Surg Oncol 25:3141-3149, 2018
6. Abraha I, Montedori A: Modified intention to treat reporting in randomised controlled trials: Systematic review. BMJ 340:c2697, 2010
7. Armijo-Olivo S, Warren S, Magee D: Intention to treat analysis, compliance, drop-outs and how to deal with missing data in clinical research: A review. Phys Ther Rev 14:36-49, 2009
8. Giuliano AE, McCall L, Beitsch P, et al: Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: The American College of Surgeons Oncology Group Z0011 randomized trial. Ann Surg 252:426, 2010
9. Wong Y, Raghavendra AS, Hatzis C, et al. Long-term survival of de novo stage IV human epidermal growth receptor 2 (HER2) positive breast cancers treated with HER2-targeted therapy oncologist. 2019;24: 313-318
10. Soran A, Ozmen V, Ozbas S, et al: Primary surgery with systemic therapy in patients with de novo stage IV breast cancer: 10-year follow-up; protocol MF07-01 randomized clinical trial. J Am Coll Surgeons 233:742-751.e5, 2021

DOI: https://doi.org/10.1200/JCO.22.00802; Published at ascopubs.org/journal/jco on July 12, 2022.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Locoregional Therapy for Intact Primary Tumor in De Novo Stage IV Breast Cancer

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Atilla Soran
Consulting or Advisory Role: Impedimed

No other potential conflicts of interest were reported.