Response to Soran et al.

To the editor:

We thank Soran et al. for their correspondence in which they raise concerns regarding two studies included in our article “Locoregional Therapy in De Novo Metastatic Breast Cancer: Systemic Review and Meta-analysis” [1]. These studies were the ABSCG-28 study [2] and the ECOG-ACRIN 2108 [3]. Most of the concerns raised were addressed in the manuscript [1]. Sensitivity analyses, including exclusion of these studies were performed to ensure the pooled estimates were robust. The inclusion of these studies did not impact on estimates.

It is important to highlight that searching of relevant grey literature, including abstracts in medical conferences is a gold standard for meta-analyses [4]. Concerns about methodologic quality should be addressed by sensitivity analysis as performed in our article [1]. Therefore, we believe data from the ECOG-ACRIN 2018, which was presented during the ASCO 2020 virtual meeting, should be included in our meta-analysis. We acknowledge the poor accrual of the ABSCG-28 trial and the interpretation that the conclusions that can be drawn from this study are limited. However, as the results of the included studies are weighted by inverse variance which is highly impacted by sampling, this trial had very limited weight in our meta-analysis. Again, we do not feel that the exclusion of this trial is appropriate as it provides further support for the inconsistent results from the other randomized trials.

Both studies included a relatively high level of positive margins (20–21%) and a large percentage of locally advanced primary breast cancers. However, patients were enrolled according to pre-defined inclusion criteria, including operability of the primary breast cancer. As such, these patients should be included in the intention to treat analyses. The high rate of positive margins reported by these studies support the limited role of locoregional therapy (LRT) in the metastatic setting.

While we acknowledge that large retrospective datasets have suggested survival benefits with LRT, these data are limited by the inherent selection bias. The best way to answer clinical questions is through randomized controlled trials and when these achieve conflicting results meta-analyses of randomized data are needed. Our meta-analysis and the more recent meta-analysis by Yu et al. [5] came to similar conclusions regarding the lack of survival benefit of LRT for most de-novo metastatic breast patients. Discrepant conclusions between retrospective, uncontrolled data and randomized trials regarding the benefits of resection of the primary in de-novo metastatic colorectal [6] and renal [7] cancers emphasize the importance of prospective studies.

The MF07-01 trial [8] is the only randomized trial included in our meta-analysis which reported survival benefit for LRT in this setting. These results might be explained by differences in tumor characteristics between study groups, a higher representation of patients with of solitary bone metastases and fewer patients with visceral disease in the LRT group. Of note, the BOMER MF 14-01, recently published by Soran et al. [9], is another randomized trial comprising only patients with bone metastases, and was not included in our study as it was published after our meta-analysis was submitted. In the BOMER MF 14-01, LRT was associated with significant improvement in overall survival [9]. Potential limitations of this study include unbalanced characteristics between the investigational and the control arms. Compared to the LRT arm, patients in the control arm had significantly more multiple bone metastases, rather than solitary or oligometastatic disease, a variable that was associated with worse outcome in a multivariate analysis reported in this study [9].

We believe that LRT for de-novo metastatic disease should not be offered routinely as weight of randomized data do not support this approach. However, we agree with Soran et al. that LRT may be suitable to selected patients, such as those with oligometastatic bone-only disease. We believe this should be assessed on a case-by-case basis. We await the results of the JCOG1017 [10] which hopefully will shed more light on this important clinical question.

References

[1] Reinhorn D, Mutai R, Yerushalmi R, et al. Locoregional therapy in de novo metastatic breast cancer: systemic review and meta-analysis. Breast 2021;58:173–81. https://doi.org/10.1016/j.breast.2021.05.003.
[2] Fitzal F, Jelic-Radisic V, Knauer M, et al. Impact of breast surgery in primary metastasized breast cancer: outcomes of the prospective randomized phase III ABSCG-28 POSITIVE trial. Ann Surg 2019;269:1163–9. https://doi.org/10.1097/SLA.0000000000002771.
[3] Khan SA, Zhao F, Solin LJ, et al. A randomized phase III trial of systemic therapy plus early local therapy versus systemic therapy alone in women with de novo stage IV breast cancer: a trial of the ECOG-ACRIN Research Group (E2108). J Clin Oncol 2020;38. https://doi.org/10.1200/JCO.2020.38.18_sup_pl_lba2. LBA2–LBA2.
[4] https://training.cochrane.org/handbook.
[5] Yu Y, Hong H, Wang Y, et al. Clinical evidence for locoregional surgery of the primary tumor in patients with de novo stage IV breast cancer. Ann Surg Oncol 2021;28:3059–70. https://doi.org/10.1245/S10434-021-09650-3.
[6] Kanematsu Y, Shitara K, Misuwa J, et al. Primary tumor resection plus chemotherapy versus chemotherapy alone for colorectal cancer patients with asymptomatic, synchronous, unresectable metastases (JCOG1007 iPACS): a randomized clinical trial. J Clin Oncol 2021;39:108–107. https://doi.org/10.1200/JCO.2020.3447.
[7] Mjean A, Ravaud A, Thezenas S, et al. Sunitinib alone or after nephrectomy in metastatic renal-cell carcinoma. N Engl J Med 2018;379:417–27. https://doi.org/10.1056/NEJMoa1803675.
[8] 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 2018;25:3141–5. https://doi.org/10.1245/s10434-018-6494-6.

[9] Soran A, Dogan L, Isik A, et al. The effect of primary surgery in patients with de novo stage IV breast cancer with bone metastasis only (protocol BOMET MF14-01): a multi-center, prospective registry study. Ann Surg Oncol 2021;28:5048–57. https://doi.org/10.1245/s10434-021-09621-8.

[10] Shien T, Nakamura K, Shibata T, et al. A randomized controlled trial comparing primary tumour resection plus systemic therapy with systemic therapy alone in metastatic breast cancer (PRIM-BC); Japan Clinical Oncology Group Study JCOG1017. Jpn J Clin Oncol 2012;42:970–3. https://doi.org/10.1093/JJCO/HYS120.

Daniel Reinhorn
Institute of Oncology, Rabin Medical Center, Petah-Tikva, Israel
Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Eitan Amir
Princess Margaret Cancer Centre, University of Toronto, Toronto, Canada

Hadar Goldvaser*
The Oncology Institute, Shaare Zedek Medical Center, Jerusalem, Israel
Faculty of Medicine, Hebrew University, Jerusalem, Israel

* Corresponding author. The Oncology Institute, Shaare Zedek Medical Center, Jerusalem, Israel.
E-mail address: hadargo@szmc.org.il (H. Goldvaser).

Available online 19 October 2021