Letters

COMMENT & RESPONSE

Adoption of Pathologic Complete Response as a Surrogate End Point in Neoadjuvant Trials in HER2-Positive Breast Cancer Still an Open Question

To the Editor The meta-analysis presented by Broglio et al[1] is an attempt to extend a previously reported pooled analysis by Cortazar et al.[2] Cortazar et al[2] estimated an individual-level association between pathologic complete response (pCR) and event-free survival (EFS), and a trial-level association between the effects of anti-human epidermal growth factor receptor 2 (HER2) therapies on pCR and EFS. Their results clearly demonstrated that there is a strong individual-level association between pCR and EFS, but virtually no association between treatment effects on these end points, which implies that no reliable prediction can be made about the effect that a new treatment will have on EFS, based on the effect of this treatment on pCR. These results applied to breast cancer in general, but doubts remained in HER2-positive disease, of which there were only few trials.

Adding a larger number of studies in HER2-positive disease, many of which are retrospective or single-arm/cohort studies, Broglio et al[1] now argue that such a prediction is possible. Toward this end, they propose to derive trial-level associations from a model that relies on the survival experience that would be expected by groups of patients with different pCR rates. This approach has no mathematical justification, as explained elsewhere.[3,4] Moreover, inspection of their Figure 3B and D allows the conclusion that the predictions (represented by the straight lines) do not fit the data (represented by the circles). Hence, one can question the validity of the model underlying the predictions. Finally, the authors argue that their predictions are in broad agreement with the observed outcomes of the ALTTO and NeoSPHERE trials, but the prediction intervals are so wide that almost any reasonable prediction would have called for a similar conclusion, something that makes their results uninformative.

For all these reasons, before a conclusion is drawn one way or another, we need more convincing statistical evidence that improvements in pCR indeed reliably predict improvements in EFS. Randomized trials with long-term follow-up will eventually provide enough data to confirm the hypothesis of Broglio et al.[1] For the benefit of patients and of clinical development of promising new drugs, we sincerely hope that their hypothesis is correct.

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