The Impact of Baseline Comorbidities and Performance Status on HER2-Targeted Therapy Outcomes

Amir Reza Akbari,[1] Benyamin Alam[2]

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Dear Editor,

We read with great interest the article by Kook et al.,[1] comparing adjuvant trastuzumab plus pertuzumab (TP) versus trastuzumab alone (T) in patients with HER2-positive breast cancer who achieved a pathologic complete response (pCR) following neoadjuvant chemotherapy. While the authors concluded that there was no significant difference in recurrence-free survival (RFS) or distant recurrence-free survival (DRFS) between the 2 regimens, we believe the study may have overlooked an important confounding variable: baseline comorbidities and performance status.

As acknowledged by the authors, the decision to use adjuvant TP in this cohort was influenced by patient and clinician discussions, taking into account factors such as relapse risk and financial constraints. However, it is plausible that patients with significant comorbidities or poorer performance status (eg, Eastern Cooperative Oncology Group [ECOG] score) were preferentially directed towards adjuvant T due to concerns about tolerability. This selection bias could have influenced survival outcomes, as patients with worse baseline health are at increased risk of recurrence and mortality independent of their adjuvant therapy regimen. For example, the PALOMA-3 trial identified ECOG performance status as a significant prognostic factor for overall survival in breast cancer patients, with ECOG 0 patients demonstrating superior survival compared to those with ECOG $\geq$1.[2]

While the study adjusted for clinical tumor size, nodal status, estrogen/progesterone receptor status, and adjuvant radiotherapy in its multivariate analyses, it did not account for baseline health indicators such as comorbidities or functional status. Prior research, including the PALOMA-3 trial, has demonstrated that these factors significantly impact survival in breast cancer patients and can confound treatment outcomes if not addressed.[2] Without incorporating such variables, there is a risk of underestimating the true efficacy of adjuvant TP in healthier patients or overestimating the equivalence of T in a potentially less fit cohort.

To strengthen the validity of their findings, we encourage the authors to conduct a posthoc analysis incorporating baseline comorbidity indices (eg, Charlson Comorbidity Index) or performance status measures. If such data are unavailable, future studies should prospectively collect and adjust for these variables to ensure a more accurate comparison of adjuvant HER2-targeted therapies.

Ethical Approval

Not applicable.

Informed Consent Statement

Not applicable.

Data availability statement

Not applicable.

Disclosure

The authors have stated that they have no conflicts of interest.

CRediT authorship contribution statement

Amir Reza Akbari: Conceptualization, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Benyamin Alam:** Conceptualization, Formal analysis, Validation, Visualization, Writing – original draft, Writing – review & editing.

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[1]King's Mill Hospital, Sherwood Forest Hospitals NHS Foundation Trust, Nottinghamshire, UK
[2]Queen Elizabeth Hospital, Birmingham, UK

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Address for correspondence: Amir Reza Akbari, MBChB, King's Mill Hospital, Mansfield Rd, Sutton-in-Ashfield, NG17 4JL Nottinghamshire, UK.
E-mail contact: amir.akbari1@nhs.net

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