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Evaluating External Validity of Oncology Biosimilar Safety Studies

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Biologics are the fastest growing medication class in the US and account for an increasing portion of health care costs. In the US, the Biologics Price Competition and Innovation Act of 2009 created an abbreviated approval pathway to expand access to safe and effective biological products.[1] Pivot et al[2] report the results of a phase 3 randomized trial of SB3, a trastuzumab biosimilar approved by the US Food and Drug Administration (FDA) in 2019, in the largest and longest follow-up study to date comparing cardiac safety and survival with its originator product, reference trastuzumab. Trastuzumab is a monoclonal antibody human epidermal growth factor receptor 2 (ERBB2) antagonist indicated for treatment of ERBB2-overexpressing breast cancer. Use of ERBB2-targeted therapy is the standard of care for patients with ERBB2-overexpressing tumors in most clinical scenarios. Despite clear clinical guidelines, previous studies indicate that up to 28% of patients with ERBB2-overexpressing early-stage breast cancer do not receive ERBB2-targeted therapy[3] and that cost of treatment is the greatest reported barrier, especially in low-income and middle-income countries.[4] In the US, there are also racial inequities, whereby Black patients, who are disproportionately burdened with financial toxicity and other structural barriers to cancer care, are less likely than their White counterparts to receive trastuzumab.[5] The entry of oncology biosimilars such as SB3 into a stable, competitive market represents a potential for cost savings and increased access to these treatments, especially among patients for whom cost is a barrier to receipt of optimal therapy. Here, we apply a health equity lens to the evaluation of biosimilar safety and consider long-term follow-up studies of oncology biosimilars and their corresponding external validity in relation to health equity. As with other medical advances, biosimilars have the potential to reduce or exacerbate health inequities depending on whether studies supporting regulatory approval exclude marginalized populations as commonly occurs, thus impacting external validity, and whether uptake remains disparate across racial and ethnic populations.

In this large phase 3 study applying dynamic block randomization,[2] participants with ERBB2-positive early or locally advanced breast cancer received either SB3 or reference trastuzumab with concomitant neoadjuvant chemotherapy and then postoperatively continued on their assigned SB3 or trastuzumab treatment as adjuvant monotherapy. The primary outcomes of this cardiac safety analysis were incidences of symptomatic congestive heart failure and asymptomatic significant decrease in left ventricular ejection fraction with a median follow-up of 68 months. The authors describe a subset of 367 participants in the phase 3 trial who were monitored for cardiac safety outcomes, wherein no symptomatic congestive heart failure was observed in either the SB3 or trastuzumab groups and only 3 asymptomatic significant left ventricular ejection fraction decreases were reported, 1 in the SB3 group and 2 in the trastuzumab group.[2] These findings are in stark contrast with the significantly increased risk of congestive heart failure (relative risk 5.11; 90% CI 3.00-8.72; $P < .00001$) and left ventricular ejection fraction decline (relative risk 1.83; 90% CI, 1.36-2.47; $P = .0008$) reported in a meta-analysis[6] of prior trastuzumab clinical trials. Pivot et al[2] note that the reasons for lower rates of cardiac events observed with SB3 in this setting include cardiac monitoring procedures with early stopping rules for participants that would preclude deterioration of cardiac function, as well as stringent inclusion criteria for the study. Accordingly, the overall prevalence of cardiovascular disease (coronary artery disease, 3.90%) and conditions representing cardiovascular risk factors (obesity, 4.46%; diabetes, 2.60%; and hypercholesterolemia, 1.12%) were very low.[2]

Although a lack of serious cardiac events observed over 5 years of follow up is reassuring, we are becoming increasingly aware of cancer treatment–related cardiotoxic effects when evaluated in clinical practice,[7] where rates of cardiovascular risk factors and cardiovascular mortality are considerably higher and disproportionately affect historically marginalized racial and ethnic groups. This study adds much needed pharmacovigilance data on Asian patients with breast cancer, a group observed to have higher risk of ERBB2-overexpressing breast cancer in the US,[8] because approximately 20% of patients in both the control and treatment groups were of Asian descent.[2] However, no Black or Latinx participants were included in this biosimilar safety analysis, and few South Asian participants were represented,[2] all of which are populations with higher rates of cardiovascular morbidity and high incidence of cardiovascular toxic effects following anti-ERBB2–targeted therapies.[7]

Readers evaluating the differences between participants included in this biosimilar phase 3 trial[2] and patients with breast cancer in clinical practice, the target population that will ultimately receive biosimilar drugs, should consider the external validity of these findings. Two aspects of external validity to be considered are generalizability and transportability. Issues with generalizability refer to concerns with making inference on the average treatment effect from a possibly biased sample of the target population back to the full target population. Transportability refers to making inference on the treatment effect for a target population when the study sample and target population do not overlap (partially or entirely). Concerns regarding cardiac safety of biosimilar cancer treatments is a challenge of transportability to a racially and ethnically diverse population with a greater prevalence of comorbidity and cardiovascular risk factors and, ultimately, the generalizability of the average treatment effect.

Data equity refers to the need for high-quality, disaggregated, and representative data of diverse racial and ethnic populations to capture inequities and underlying sociostructural factors associated with health outcomes. Without data equity, evidence used to inform public policies, including drug approvals, fails to capture the diverse experiences and needs of the full population affected by the disease. Explicitly, a lack of data equity, including inadequate representation, across racial and ethnic groups in biomedical research is a root cause of persistent health inequities in the US, because clinical trials have historically provided disparate access to investigational therapies, resulting in limited transportability of study findings. In 2022, the US FDA released draft guidance on diversity plans to improve enrollment of participants from historically excluded racial and ethnic populations in clinical trials.[9] This guidance will represent a mandate for drug sponsors as of 2024 (Public Law 117-328). The lack of transportability of findings from even the study by Pivot et al,[2] the largest ever biosimilar safety trial reporting on long-term cardiac outcomes in ERBB2-overexpressing breast cancer, highlights the importance of efforts by the FDA to improve the diversity of clinical trials at their inception or through postmarketing requirements. Leveraging empirical data is increasingly recognized as a means to address gaps in data equity that, as demonstrated here, still remain despite decades of follow-up of the originator biologic reference product and the introduction of multiple biosimilars. In addition to expanding safety and efficacy data among patient populations that are frequently excluded from clinical trials and improving the generalizability and transportability of study findings, the use of empirical data has the potential to affect clinical trial diversity during initial study design. For example, assessing the impact of eligibility criteria in cohorts of patients treated in clinical practice, in advance of study conduct, can optimize enrollment of participants from historically excluded racial and ethnic populations and prioritize health equity early in the prospective evidence generation life cycle.[10]

In summary, we commend Pivot et al[2] for execution of this global biosimilar safety analysis of SB3 with an impressive 6 years of follow-up. The investigators provide important evidence further establishing the comparability of a widely used biosimilar treatment for ERBB2-overexpressing early breast cancer in a sample of predominantly White and Asian patients. However, this study lacks external validity for Black and Latinx patients, who are at higher risk of cardiovascular toxic effects, have the least access to ERBB2-targeted therapy, and may have the greatest potential benefit from

increased affordability.[3,5,8] We highlight the potential of empirical data for retrospective and prospective evidence generation to address a root cause of persistent cancer health inequities.

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