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Editorial

EDITORIAL

On the Quest of Risk Stratification in HER2-Positive Breast Cancer

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The recognition that breast cancer is a heterogeneous disease has led to research efforts to identify patient subgroups with distinct risk profiles. Nowadays, breast cancer is broadly divided into categories on the basis of expression of the estrogen receptor, progesterone receptor, and HER2, and modern drug development paradigm has shifted to focusing on treatment strategies tailored toward these subtypes. Approximately 10%-20% of breast cancers have overexpression of HER2 protein. HER2-targeted therapies have drastically improved survival outcome for patients with early-stage HER2-positive breast cancer; many patients are cured with the combination of chemotherapy and trastuzumab. Recent years have seen an increase in the use of neoadjuvant therapies. Multiple studies have reported a strong correlation between pathologic complete response (pCR) and long-term outcomes (1-3). It is widely accepted that patients with residual disease after neoadjuvant HER2-directed therapy confer worse outcomes. Recent research has focused on strategies to deescalate the extent of therapy (by decreasing the amount of chemotherapy or the duration of trastuzumab) in low-risk patients. To this end, a multitude of investigations are ongoing to discover molecular biomarkers that can identify a subset of patients with excellent prognosis to avoid overtreatment.

In this issue of the Journal, Chic and colleagues (4) investigated the association between a novel biomarker, CelTIL, and long-term clinical outcomes. A total of 196 tumor samples from the NeoALTTO phase III trial were included in the study. CelTIL score was determined based on tumor infiltrating lymphocytes (TILs) and tumor cellularity measured in a tumor biopsy after 2 weeks of neoadjuvant anti-HER2 therapy. After adjustment for baseline TILs, tumor size, nodal status, hormone-receptor status, surgery, treatment arms, and pCR, CelTIL remained statistically significantly associated with event-free survival and overall survival in multivariable Cox proportional hazards models. The investigators also evaluated the prognostic value of CelTIL by pCR status, although as the authors aptly noted, these findings were inconclusive because of limited sample size. The authors soundly concluded that future validations are needed.

Although the results appear promising, issues pertaining to limitations of the dataset warrant further consideration. First, a most notable limitation is the modest sample size. Although the data were from a randomized clinical trial, the good prognosis of the study population limits the observed number of events. With a time-to-event outcome, the power to discern a biomarker prognostic effect depends on the event number. In the subgroup analysis investigating the prognostic strength of CelTIL among patients who achieved pCR, for example, there were only 27 event-free survival events (Figure 1, E) (4). Although the estimated hazard ratio of 0.48 suggests a more favorable outcome for patients with high CelTIL, the uncertainty of this estimate is reflected in the wide confidence interval (95% confidence interval = 0.11 to 2.12) and a statistically nonsignificant *P* value ($P = .33$). In fact, the data did not provide robust evidence to support the prognostic value of CelTIL in either pCR subgroup (Figure 1, E and F). It is equally important to note that the lack of a statistically significant *P* value does not establish the absence of a prognostic effect (ie, failing to reject the null does not imply acceptance of the null); it is merely indicative of the lack of statistical evidence to rule out the possibility that the biomarker has no prognostic effect. The assumption of the multivariable statistical modeling must also be recognized. Specifically, adjusting for pCR status makes the assumption that the prognostic effect of CelTIL is the same for patients who achieved pCR and those who did not. Additionally, after adjusting for other clinicopathologic variables, pCR was no longer a statistically significant prognosticator for long-term outcomes in the presence of CelTIL (Supplementary Table 2). The instability of the results further highlights the challenges of obtaining robust evidence in a limited dataset and underscores the importance of further validations in large independent datasets.

Second, the study demonstrates the association of CelTIL with clinical outcomes (prognostic) but not the predictive value. To establish the predictive utility of CelTIL, data from randomized trials with at least 2 different treatment regimens will be required. In particular, a biomarker is predictive if the treatment effect is different for biomarker-positive patients compared with biomarker-negative patients (5,6). For example, if one can demonstrate that patients with low CelTIL scores respond more favorably to dose escalation (eg, compared with standard trastuzumab-based therapy) than patients with high CelTIL scores, then the predictive claim for CelTIL may be in order. Of

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note, statistical evaluation of the predictive value of a biomarker entails testing for the interaction between treatment group and the biomarker in question. The required sample size to test whether an interaction is statistically significant is often much larger than that required for testing a prognostic effect (7,8). These validations may be best performed in prospective-retrospective settings using tissue specimens and clinical outcome data collected in completed randomized clinical trials (9).

Finally, for the biomarker assay to be deployed in clinical practice, the test will need to be run in a Clinical Laboratory Improvement Amendments–certified laboratory to ensure that molecular biomarkers such as TILs and CelTIL can be accurately and reproducibly ascertained. In particular, standardization of the laboratory methodology as well as demonstration of acceptable preanalytical and analytical performance of the assay will be vital toward this goal.

As the armamentarium of effective therapies for HER2-positive breast cancer continues to expand, we need better ways to stratify patients for tailored treatment decision making. The study by Chic et al. (4) offers a promising tool that integrates molecular biomarkers and patient factors for individual risk stratification. Hopefully, with rigorous validations, we can further our goal of achieving precise risk stratification for patients with HER2-positive breast cancer. Furthermore, novel tools like this will be critical to the design of future clinical trials hoping to deescalate adjuvant therapies.

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