

EDITORIALS



DESTINY-Changing Results for Advanced Breast Cancer

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The implications of the results of the DESTINY-Breast04 trial reported by Modi et al.¹ in this issue of the *Journal* are difficult to overstate. Immediately practice-changing, these data show that a human epidermal growth factor receptor 2 (HER2)-directed therapy, trastuzumab deruxtecan, leads to significant and striking improvements in both progression-free survival and overall survival as compared with chemotherapy among patients with metastatic breast cancer with low expression of HER2. Consistent benefit was observed in patients with poor prognostic indicators, including triple-negative cancer. Although the trophoblast cell-surface antigen 2 (Trop-2)-targeted antibody-drug conjugate sacituzumab govitecan has improved outcomes in patients with heavily pretreated triple-negative disease, the median progression-free survival of just under 6 months and overall survival of approximately 1 year² are lower than those reported in the 40 patients with triple-negative disease treated with trastuzumab deruxtecan (8.5 months and 18.2 months, respectively). A randomized trial is, of course, needed to compare these two agents, and sequencing studies are required to address whether cross-resistance develops among antibody-drug conjugates comprising similar cytotoxic payloads like those in sacituzumab govitecan and trastuzumab deruxtecan.

One critical question generated by these data is the threshold of HER2 expression needed for antitumor activity with trastuzumab deruxtecan. It is interesting that no clear evidence suggests that the level of expression determined by an immunohistochemical (IHC) assay is associated with benefit from trastuzumab deruxtecan. In the DESTINY-Breast04 trial, outcomes were similar

in patients with a score of 1+ on IHC analysis and those with a score of 2+. Furthermore, promising antitumor activity was observed with trastuzumab deruxtecan in tumors without any detectable HER2 on IHC analysis in the DAISY trial.³ Although false negative results or heterogeneous expression might explain this finding, another possibility is that the level of HER2 expression required for activity of trastuzumab deruxtecan is lower than the sensitivity of the IHC assay. Indeed, ubiquitous low expression of HER2 (on the basis of messenger RNA and protein) has been reported in all breast cancers.⁴ If breast cancers all express enough HER2 for trastuzumab deruxtecan to have efficacy, then a reliable test for low expression of HER2 is unnecessary.

Herein lies the dilemma. In order to know the threshold of expression for sensitivity to trastuzumab deruxtecan, a reliable, sensitive quantitative assay is needed.

In the DESTINY-Breast04 trial, central confirmation of HER2 expression was evaluated by means of IHC assay with the use of the VENTANA HER2/neu (4B5) antibody, which reportedly cross-reacts with proteins such as HER4 and ZSCAN18 and thus has the potential to result in overestimation of HER2 expression.⁵ Concordance between local and central IHC assessment from the DESTINY-Breast04 trial has not been reported. However, interlaboratory variability with HER2 IHC results is well recognized. In one analysis in which 5 pathologists scored IHC-stained samples of HER2-nonamplified breast cancer, concordance was only 65%, with 15% of the pathologists disagreeing between HER2 1+ as compared with 0.⁶ Another investigation showed a 26% concordance for 0 and 1+ among 18 patholo-

gists.⁷ These results are not surprising, because IHC testing was not intended to accurately quantify low levels of protein expression, and doing so has not been a clinically meaningful endeavor thus far. Currently, an assay to reliably and sensitively assess low levels of HER2 expression does not seem to exist. This should be among the highest priorities now.

Finally, a word about safety. The adverse events observed in the DESTINY-Breast04 trial were generally similar to those previously reported with trastuzumab deruxtecan,⁸ with the notable exception of cardiac toxic effects. In the DESTINY-Breast04 trial, left ventricular dysfunction was reported in close to 4.6% of the patients who received trastuzumab deruxtecan, with one grade 3 event and two events involving symptomatic heart failure. A total of 11.9% of the patients had a 10 to 19% decrease from baseline in ejection fraction, and 1.5% of the patients had more than a 20% decrease from baseline. In the DESTINY-Breast03 trial, fewer than 3% of the patients with HER2-positive disease who received trastuzumab deruxtecan had a decrease in ejection fraction, and all events were asymptomatic.⁸ Selection bias may account for the low incidence of cardiomyopathy in the DESTINY-Breast03 trial, because all the patients had received previous HER2-directed therapies without the development of cardiomyopathy. Differences in unmeasured baseline risk factors may also account for the seemingly discrepant cardiac outcomes. To this point, the proportion of patients with anthracycline pretreatment was reported in neither trial. With more widespread use of nonanthracycline options for HER2-positive early breast cancer,^{9,10} the proportion of patients with cardiomyopathy from HER2-directed therapy may be decreasing. In contrast, use of anthracycline agents for high-risk, HER2-negative, early disease remains standard, which has the potential to increase the risk of cardiac events with a HER2-targeted approach.

The results of the DESTINY-Breast04 trial will undoubtedly translate into a new therapeutic option for nearly half the patients who receive a diagnosis of metastatic breast cancer, an extraordinary finding given that no HER2-targeted agent has shown this type of benefit in HER2-nonamplified, nonoverexpressing breast cancer until now. These results should inspire scientists to begin the rigorous yet critically important translational components of this trial, including efforts to accurately identify those patients who are most likely to benefit.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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