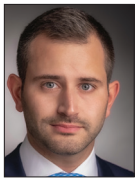
BREAST CANCER IN FOCUS

Current Developments in the Management of Breast Cancer

Section Editor: Hope S. Rugo, MD

Lessons From Recent Trials of Antibody-Drug Conjugates in Breast Cancer



Paolo Tarantino, MD
Clinical Research Fellow
Dana-Farber Cancer Institute
Boston, Massachusetts

H&O Could you describe the activity and safety results of the DESTINY-Breast04 trial?

PT DESTINY-Breast04 was a landmark phase 3 trial that compared trastuzumab deruxtecan, also known as T-DXd (Enhertu, Daiichi-Sankyo/AstraZeneca), with traditional chemotherapy for patients who had pretreated, human epidermal growth factor receptor 2 (HER2)–low metastatic breast cancer. T-DXd is an anti-HER2 antibody-drug conjugate (ADC). The choice of chemotherapy regimen was left to the treating physician and could include taxanes, eribulin, capecitabine, or gemcitabine. Dr Shanu Modi presented the results, which were simultaneously published in the *New England Journal of Medicine*, at the 2022 American Society of Clinical Oncology (ASCO) annual meeting.

Patients were eligible for the trial if they had received 1 or 2 lines of previous chemotherapy, as well as endocrine therapy if they had hormone receptor (HR)–positive disease. They were also required to have HER2-low disease, which was defined as either a score of 1+ on immunohistochemistry (IHC) or an IHC score of 2+ plus negative results on in situ hybridization (ISH). IHC results were based on the most recent biopsy, a previous biopsy, or even the primary tumor.

A total of 557 patients underwent randomization in a 2:1 ratio to T-DXd or traditional chemotherapy. Most patients (88.7%) had HR-positive disease; the remaining 11.3% had HR-negative disease.

The investigators found that for all patients, the median progression-free survival (PFS) was nearly doubled in the T-DXd group vs the traditional chemotherapy group, at 9.9 vs 5.1 months, respectively. This difference represented improvement that was both statistically significant and clinically meaningful. Overall survival (OS) was also significantly better in the T-DXd group vs the traditional chemotherapy group, at 23.4 vs 16.8 months, respectively—an absolute difference of 6.6 months. This was truly remarkable because we do not frequently see improvements in OS in this setting, particularly in a first analysis of study results—so these were very important findings.

Results were similar in the HR-positive cohort, in which the median PFS was 10.1 months with T-DXd vs 5.4 months with traditional chemotherapy and OS was 23.9 months vs 17.5 months, respectively—a difference of 6.4 months.

The safety profile of T-DXd in this trial was similar to what we have seen with this agent in HER2-positive disease, for which it received approval in 2019. One problem is that patients experience off-target side effects from the chemotherapy payload delivered by the ADC. We did see a fair amount of nausea and vomiting, both of which are very important to address. Fortunately, we are getting better at managing these side effects with prophylactic antiemetics. Fatigue was also common with T-DXd in this trial. In addition, hematologic toxicities such as neutropenia and anemia occurred with T-DXd, but less often than with traditional chemotherapy.

The most concerning adverse event with T-DXd remains interstitial lung disease (ILD). This is usually

grade 1 or 2 when it occurs, but ILD led to 3 fatalities in this study. As a result, patients receiving T-DXd must have scans every 6 to 12 weeks to monitor their lung function. Another adverse event of special concern is cardiotoxicity, so it is important to monitor the left ventricular ejection fraction in these patients. Fortunately, a decrease in the left ventricular ejection fraction occurred in fewer than 5% of the patients in this study.

H&O Could you further discuss what made the results of this trial remarkable?

PT Beyond the impressive improvements in outcomes observed in the trial, I believe it is important to stress that the HER2-low population that was enrolled in DESTINY-Breast04 reflects a very large population of patients in clinical practice—at least half of patients with metastatic breast cancer. This includes patients with HR-positive disease, as well as many patients with HR-negative (ie, triple-negative) disease. Now that T-DXd is approved for use in patients with HER2-low metastatic breast cancer, as of August 5 of this year, many patients can benefit from this agent. The most recent guidelines from the National Comprehensive Cancer Network (NCCN) recommend T-DXd for patients with HER2 IHC 1+ or 2+/ISH-negative metastatic breast cancer who have received prior chemotherapy.

H&O How and when should HER2 status be determined?

PT This is a critical question because we currently have no data or official guidance regarding evaluation of HER2 status. We know that a tumor can be HER2-low on an early biopsy and HER2-negative on a later biopsy, but we do not know how to categorize patients with discordant results. We do know that patients were eligible for the DESTINY-Breast04 trial on the basis of HER2-low results from a recent biopsy, a past biopsy, or even the primary tumor. The way I personally interpret the data is to consider a patient eligible for T-DXd who has a HER2-low result on any prior assessment during the course of disease. That said, my approach is based on intuition rather than data. We expect to see data regarding when to assess HER2 expression during a presentation by Dr Aleix Prat of Barcelona at the 2022 San Antonio Breast Cancer Symposium (SABCS), in which he will discuss the biomarker data from DESTINY-Breast04.

H&O Could you describe the activity and safety results of the TROPiCS-02 trial?

PT The TROPiCS-02 trial is another study that has revolutionized the way we treat metastatic breast cancer. This randomized phase 3 trial enrolled patients with HR-positive metastatic breast cancer who had received at least 2 to 4 prior lines of chemotherapy. All patients had also received endocrine therapy and treatment with cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, so this population was highly pretreated. A total of 541 patients were randomly assigned in a 1:1 ratio to receive either the Trop-2–directed ADC sacituzumab govitecan (Trodelvy, Gilead) or traditional chemotherapy.

The ASCENT trial had already shown that sacituzumab govitecan improves both PFS and OS in comparison with traditional chemotherapy in patients with pretreated triple-negative breast cancer, so it was great to see that sacituzumab govitecan also improved outcomes in HR-positive patients in TROPiCS-02. In results that Dr Hope Rugo presented at the 2022 ASCO annual meeting, sacituzumab govitecan improved median PFS from 4.0 to 5.5 months, an absolute difference of 1.5 months (hazard ratio, 0.66; *P*=.0003). In updated results that Dr Rugo presented at the 2022 European Society for Medical Oncology (ESMO) congress, sacituzumab govitecan also improved median OS from 11.2 to 14.4 months, an absolute difference of 3.2 months (hazard ratio, 0.79; *P*=.02).

> When we have more data, we will be able to see if bispecific ADCs are more effective than simple ADCs.

In terms of side effects, sacituzumab govitecan confirmed what we see every day in the clinic when treating patients with triple-negative breast cancer. The main toxicities in this trial were neutropenia, nausea, fatigue, and diarrhea, with grade 3 or higher adverse events occurring in 74% of the patients on sacituzumab govitecan and 60% of the patients on traditional chemotherapy. However, sacituzumab govitecan was more effective than traditional chemotherapy at preserving quality of life.

On the basis of these encouraging results, the NCCN guidelines now recommend sacituzumab govitecan for use in HR-positive/HER2-negative breast cancer (a category 2A recommendation, before survival data were available),

in addition to recommending it in triple-negative disease (a category 1 recommendation).

H&O Would you say that the OS improvement in TROPiCS-02 was clinically meaningful?

PT Absolutely. Although the OS advantage of 3.2 months seen with sacituzumab deruxtecan was shorter than the advantage of 6.6 months seen with T-DXd, the patients in TROPiCS-02 were highly pretreated and had all received CDK4/6 inhibitors. Nearly all the patients—95%—had visceral disease, so this was a very high–risk population. In this setting, we usually use single-line chemotherapy agents, which have a poor response rate and a short PFS as observed in the control arms of both DESTINY-Breast04 and TROPiCS-02.

H&O How should T-DXd and sacituzumab govitecan be sequenced?

PT This question is difficult to answer for 2 reasons. First, we do not have head-to-head comparisons between T-DXd and sacituzumab govitecan, so we are forced to rely on cross-trial comparisons. Second, we do not have much data regarding the activity of these drugs when they are sequenced. Still, we can use the enrollment criteria of the studies to better understand how to use the drugs. For example, in DESTINY-Breast04, T-DXd was used in patients with HER2-low metastatic breast cancer who had received a minimum of 1 prior line of chemotherapy, and this is the way the US Food and Drug Administration approved the drug. But in TROPiCS-02, the patients had received a minimum of 2 prior lines of chemotherapy and a maximum of 4 prior lines before sacituzumab govitecan. As a result, my instinct would be to use T-DXd first, after 1 prior line of chemotherapy, and sacituzumab govitecan next, after 2 prior lines of chemotherapy.

The question of sequencing is slightly more complicated in triple-negative disease because there is no evidence favoring either ADC after 1 or more prior lines of chemotherapy. I would say that either T-DXd or sacituzumab govitecan could be used after chemotherapy in triple-negative disease.

In some cases, the decision will come down to the patient's comorbidities and preferences. If the patient has a respiratory comorbidity, sacituzumab govitecan may be favored first because of concerns about ILD with T-DXd. If the patient is especially concerned about hair loss, T-DXd may be preferred, given the lower rates of alopecia. We are doing preliminary work at Dana-Farber to design trials that will tell us which agent to use first. Also, we are conducting an ongoing phase 2 trial at Dana-Farber to see whether scalp cooling can help to reduce the rate of alopecia with agents that include T-DXd and sacituzumab govitecan (NCT04986579). In most cases, though, the best way to select the first treatment is based on the enrollment criteria of DESTINY-Breast04 and TROPiCS-02. We hope to have better biomarkers in the future to tell us which agents will be most effective in certain patients.

H&O What other ADCs are in the pipeline for breast cancer?

PT The ADCs that have shown the most intriguing activity in metastatic breast cancer are patritumab deruxtecan, also known as HER3-DXd, and datopotomab deruxtecan, also known as Dato-DXd.

HER3-DXd is similar to T-DXd but is directed to HER3 instead of HER2. At the 2022 ASCO annual meeting, Dr Ian Krop presented the results of a phase 1/2 trial that looked at this agent in every subtype of metastatic breast cancer—HR-positive, triple-negative, and even HER2-positive (NCT02980341). The objective response rate to HER3-DXd was 23% to 43%, depending on the subtype, and the duration of response ranged from 6 to 8 months. These data suggest that there might be a benefit in targeting HER3 with an ADC. We expect to see more data from phase 2 trials of this agent.

Dato-DXd is similar to sacituzumab govitecan in that it targets TROP-02 and is similar to T-DXd in that it uses the same payload. In data from the phase 1 TROPION-PanTumor01 trial, which Dr Krop presented at the 2021 SABCS, the objective response rate in patients with triple-negative breast cancer who had not received a prior ADC was 52% (NCT03401385). In some cases, responses were seen in patients who had received prior sacituzumab deruxtecan or prior T-DXd. This compound is now being tested in phase 3 trials of patients with HR-positive disease (TROPION-Breast01; NCT05104866) and patients with triple-negative disease (TROPION-Breast02; NCT05374512). Both these agents have the potential to enlarge the pipeline of available ADCs in clinical practice.

In addition, new types of ADCs are being designed, including zanidatamab zovodotin, also known as ZW49. The payload in ZW49 is linked not to a simple monoclonal antibody but to a bispecific monoclonal antibody that binds 2 different epitopes of HER2—the epitopes to which trastuzumab and pertuzumab (Perjeta, Genentech) normally bind. In preliminary data from a phase 1 study of ZW49, which Dr Komal Jhaveri presented at the 2022 ESMO congress, the objective response rate at the recommended phase 2 dose (2.5 mg/kg every 3 weeks) was 31% among 29 patients with a variety of HER2-

positive solid tumors, including breast cancer. When we have more data, we will be able to see if bispecific ADCs are more effective than simple ADCs.

Additional compounds for which we have promising preclinical data include immunotherapy-based ADCs and radionuclide-based ADCs, in which radioactive particles are delivered selectively to tumor cells. ADCs are modular, so we are learning that we can change the various components of ADCs—the antibody, the linker, and the payload—to develop novel agents with improved activity, safety, and tolerability.

H&O Are ADCs being tested in earlier-stage breast cancer?

PT We are curious to see what will happen when ADCs are used in the setting of earlier-stage disease, in which they might have an even larger effect. Two phase 3 trials in earlier HER2-positive disease are already ongoing: DESTINY-Breast05, which is looking at T-DXd as adjuvant therapy in nonmetastatic breast cancer (NCT04622319), and DESTINY-Breast11, which is looking at T-DXd as neoadjuvant therapy in early-stage disease (NCT05113251).

Finally, a phase 3 trial called SASCIA is looking at the use of adjuvant sacituzumab govitecan in patients with nonmetastatic HER2-negative breast cancer (NCT04595565) who do not have a complete pathologic response to neoadjuvant treatment.

H&O What other important studies of ADCs are ongoing in metastatic breast cancer?

PT The phase 2 TALENT trial is looking at the use of neoadjuvant T-DXd in HER2-low, HR-positive metastatic breast cancer; we expect to see early results presented at the 2022 SABCS (NCT04553770).

H&O Is there anything you would like to add?

PT We are seeing that ADCs are more effective than traditional chemotherapy, but they are not necessarily less toxic. We are especially concerned about ILD with T-DXd and about neutropenia—which can be severe—with sacituzumab govitecan. We need to be attentive to managing side effects when we use ADCs.

Disclosure

Dr Tarantino has served as advisor or consultant for AstraZeneca, Daiichi Sankyo, and Lilly.

Suggested Readings

Jhaveri K, Han H, Dotan E, et al. Preliminary results from a phase I study using the bispecific, human epidermal growth factor 2 (HER2)-targeting antibody-drug conjugate (ADC) zanidatamab zovodotin (ZW49) in solid cancers [ESMO abstract 460MO]. *Ann Oncol*. 2022;33(7)(suppl).

Bardia A, Hurvitz SA, Tolaney SM; ASCENT Clinical Trial Investigators. Sacituzumab govitecan in metastatic triple-negative breast cancer. *N Engl J Med*. 2021;384(16):1529-1541.

Krop I, Juric D, Shimizu T, et al. Datopotamab deruxtecan in advanced/metastatic HER2- breast cancer: results from the phase 1 TROPION-PanTumor01 study [SABCS abstract GS1-05]. *Cancer Res*. 2021;81(4)(suppl).

Krop IE, Masuda N, Mukohara T, et al. Results from the phase 1/2 study of patritumab deruxtecan, a HER3-directed antibody-drug conjugate (ADC), in patients with HER3-expressing metastatic breast cancer (MBC) [ASCO abstract 1002]. *J Clin Oncol*. 2022;40(16)(suppl).

Modi S, Jacot W, Yamashita T; DESTINY-Breast04 Trial Investigators. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. *N Engl J Med*. 2022;387(1):9-20.

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines ®). Breast Cancer. v.4.2022. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Updated June 21, 2022. Accessed November 7, 2022.

Rugo HS, Bardia A, Marmé F, et al. Overall survival (OS) results from the phase III TROPiCS-02 study of sacituzumab govitecan (SG) vs treatment of physician's choice (TPC) in patients (pts) with HR+/HER2- metastatic breast cancer (mBC) [ESMO abstract LBA76]. *Ann Oncol*. 2022;33(5)(suppl).

Rugo HS, Bardia A, Marmé F, et al. Primary results from TROPiCS-02: a randomized phase 3 study of sacituzumab govitecan (SG) versus treatment of physician's choice (TPC) in patients (pts) with hormone receptor–positive/HER2-negative (HR+/HER2-) advanced breast cancer [ASCO abstract LBA1001]. *J Clin Oncol*. 2022;40(17)(suppl).

Rugo HS, Bardia A, Marmé F, et al. Sacituzumab govitecan in hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol*. 2022;40(29):3365-3376.