# BREAST CANCER IN FOCUS

Current Developments in the Management of Breast Cancer

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## Update on Antibody-Drug Conjugates in Breast Cancer

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**H&O** How do antibody-drug conjugates (ADCs) work?

**HR** These anticancer drugs have a fascinating construct that combines an antibody, a toxin, and a linker. The idea is to use a "smart bomb" approach in which a unique antigen that is expressed on cancer cells, but less or not at all on normal cells, is targeted by using the corresponding antibody. The antibody binds to the cancer cell, and the ADC becomes internalized. After the ADC enters the vesicle of the cell, it is digested, and the linker releases the toxin into the cancer cell.

We want to have the biggest "bang for the buck" with these toxins, so researchers choose agents that are highly toxic in very small amounts and that would not be safe given as naked drugs. By using a linker to attach the toxin to the antibody, we are able to deliver small amounts of the toxin directly to the cancer cells. This approach can be highly effective.

A critical aspect of ADCs is using the right linker. The linker needs to be digested after it enters the cancer cell so that it can release the drug directly to the cell. If the linker is digested too early, we end up with systemic drug administration. It took some time to develop the current generation of linkers, and improvements are ongoing.

A final important feature of ADCs is their ability to kill cells that are adjacent to cancerous cells, which is known as the *bystander effect*. Even if these neighboring cells do not express the target antigen in large amounts, they can pose a threat by being part of the tumor environment. Bad-actor cells like to keep company with one another. A toxin that has the ability to pass through the cell membrane holds the potential to kill bystander cells at the same time that the ADC kills the antigen-expressing cells.

The first ADC to receive US Food and Drug Administration (FDA) marketing authorization was gemtuzumab ozogamicin (Mylotarg, Pfizer), which was approved in 2000 for treating acute myeloid leukemia. The first ADCs to receive FDA approval in breast cancer were the second-generation agents trastuzumab emtansine, also known as T-DM1 (Kadcyla, Genentech), in February 2013, and trastuzumab deruxtecan (Enhertu, Daiichi-Sankyo/AstraZeneca), in December 2019. The third-generation agent sacituzumab govitecan-hziy (Trodelvy, Immunomedics) received FDA approval in April 2020. One advantage of the newer agents over first-generation ADCs is that technologic improvements have made it possible to increase the drug-to-antibody ratio (DAR).

**H&O** Can you describe T-DM1 in more detail?

**HR** T-DM1 consists of trastuzumab linked to a derivative of maytansine, which is a microtubule antagonist. The DAR is relatively low, at about 3.5:1. Trastuzumab given by itself is relatively nontoxic, except for its known cardiac toxic effects and rare infusion reactions. T-DM1 is associated with additional toxicities attributable to the toxin; these include elevated transaminases, thrombocytopenia, and generally mild nausea. With longer exposure, mild neuropathy—which appears to be self-limited—has been seen. Interestingly, given the

experience with the newer ADCs, which have higher DARs, essentially no clinical alopecia is seen with T-DM1.

**H&O** What are the main studies looking at T-DM1?

**HR** T-DM1 is highly effective in human epidermal growth factor receptor 2 (HER2)–positive disease. In the EMILIA study, which led to the approval of T-DM1, the drug improved response, progression-free survival (PFS), and overall survival (OS) vs lapatinib/capecitabine in patients who had metastatic HER2-positive disease and had previously received trastuzumab and a taxane. In the more-recent TH3RESA study, T-DM1 continued to improve these parameters vs physician's choice of treatment in patients with metastatic HER2-positive disease that had progressed after at least 2 previous anti-HER2 regimens.

It is quite exciting to see T-DM1 being repurposed in the adjuvant setting. The most successful approach, which received FDA approval in May 2019, has been in patients with HER2-positive early breast cancer who have residual disease after neoadjuvant taxane- and trastuzumab-based treatment. The 3-year data from the KATHERINE trial, in which 70% of the patients had hormone receptor–positive, HER2-positive early breast cancer, showed a marked improvement in invasive disease–free survival with this approach. In addition, T-DM1 was quite well tolerated in KATHERINE, with most participants able to complete all 14 doses. This was a clinically important new advance in the treatment of early-stage HER2-positive breast cancer. We are still waiting to see longer-term disease-free data as well as initial OS data from this trial.

T-DM1 also has been studied in the neoadjuvant setting. The ADAPT trial (n=350) from the West German Study Group showed an excellent pathologic complete response rate of about 41% with just 4 preoperative doses of T-DM1 in patients with hormone receptor–positive, HER2-positive disease. More recently, Harbeck and colleagues presented data at the 2020 European Society for Medical Oncology (ESMO) Virtual Congress showing that patients who had a pathologic complete response enjoyed excellent disease-free survival (DFS) after surgery; all patients completed 1 year of trastuzumab.

Finally, the ATEMPT trial looked at the use of T-DM1 in patients with stage I, node-negative, HER2-positive disease. Participants were randomly assigned in a 3:1 ratio to 1 year of T-DM1 every 3 weeks—a long course for stage I disease—or 12 weeks of paclitaxel plus 1 year of trastuzumab, the so-called APT or TH regimen. The primary endpoints were 3-year DFS and safety; the trial was to powered to evaluate the efficacy of TH or to compare the efficacy of the 2 arms. According to results presented by Tolaney and colleagues at the 2019 San Antonio Breast Cancer Symposium (SABCS), the 3-year DFS rate was 97.7% for T-DM1, with just 10 events (2 of which were distant events) in the 382 patients enrolled in that arm. About 17% of patients were unable to complete the entire year of therapy, stopping early because of adverse events such as mild nausea, fatigue, and mild neuropathy. Overall, 75% of patients had hormone receptor–positive disease, so clearly longer follow-up is needed to estimate DFS fully. Patients did not experience hair loss, and at the 18-month point, patients in the T-DM1 group had less amenorrhea and neuropathy than did those in the APT group.

A study is planned (ATEMPT 2.0) to compare 6 months of T-DM1 followed by 6 months of trastuzumab vs the TH regimen as adjuvant treatment in 500 patients with stage I, HER2-positive breast cancer—to reduce cumulative toxicity but maintain efficacy.

In addition to the data described above, analyses of data from the EMILIA study, along with several small studies in patients with brain metastases, suggest that T-DM1 may have some efficacy against brain metastases. T-DM1 in combination with the oral tyrosine kinase inhibitor tucatinib (Tukysa, Seagen) is being compared with T-DM1 in combination with placebo in patients who have metastatic HER2 positive breast cancer (HER2CLIMB-02, NCT03975647). Tucatinib in combination with capecitabine and trastuzumab has shown striking effects in patients with HER2-positive brain metastases vs capecitabine and trastuzumab alone, and the triplet has been approved for the treatment of metastatic HER2-positive breast cancer.

**H&O** Can you describe trastuzumab deruxtecan in more detail?

**HR** Trastuzumab deruxtecan, which is also known as fam-trastuzumab deruxtecan-nxki, received accelerated approval in December 2019, on the basis of initial data from a phase 1b/2 trial, for patients with unresectable or metastatic HER2-positive breast cancer previously treated with 2 or more anti-HER2–based regimens in the metastatic setting. T-DXd is a novel ADC in which a conjugate of a trastuzumab biosimilar is linked to the novel topoisomerase I inhibitor deruxtecan, which is an exatecan derivative. Trastuzumab deruxtecan has a relatively high DAR of approximately 8:1. It is also membrane-permeable, a feature thought to enable a bystander effect—the killing of nearby cells.

Trastuzumab deruxtecan was first tested in a dose escalation study in patients who had disease resistant to T-DM1. With increasing doses, an increase in toxicity, especially pulmonary toxicity, was seen. Further evaluation

of 2 doses led to adoption of the lowest dose, 5.4 mg/kg, for further dose expansion, and a total of 180 patients with HER2-positive disease that had progressed on prior HER2-targeted therapies, including T-DM1, were enrolled. Like trastuzumab emtansine, T-DXd is given every 3 weeks. Efficacy data in 168 patients were remarkable; the disease of all but 4 patients showed at least some decrease in size. The overall response rate was 62.4%, with a median duration of response of 20.8 months.

The initial data that led to approval, published by Modi and colleagues in the *New England Journal of Medicine* in 2020, reflected a median follow-up of 11.1 months and reported a median PFS of 16.4 months. The same group presented updated data at the 2020 SABCS reflecting a median follow-up of 20.5 months; they reported a median PFS of 19.4 months and a median OS of just under 25 months. These exciting data suggest that T-DXd is highly effective, achieving durable responses in patients who have already received our best HER2-targeted therapy in the metastatic setting.

The toxicities of this drug included all grades of nausea in approximately 80% of people, although fewer than 10% had grade 3 or higher nausea. In my experience, many patients need nausea medication for home use following the infusion. Approximately 40% of patients experienced grade 1/2 vomiting; grade 3 emesis was uncommon.

Trastuzumab deruxtecan can also cause low-grade diarrhea. Approximately 20% of patients had grade 3 or higher neutropenia, which was managed with dose reductions and occasionally growth factor use or dose delay. Grade 3 thrombocytopenia was seen in fewer than 5% of patients. Trastuzumab deruxtecan causes alopecia in approximately 50% of patients—mostly grade 1, or hair thinning—rather than complete hair loss. The thinning progresses as treatment continues, but most of my patients treated with trastuzumab deruxtecan keep more than half of their hair. We do not see alopecia with T-DM1, but we do see it with the newer-generation ADCs, possibly because of the higher DARs and the bystander effect.

The most striking and important toxicity seen with trastuzumab deruxtecan is interstitial lung disease (ILD), which occurred in 15.2% of patients, according to updated data presented by Modi and colleagues at the 2020 SABCS. We have learned how to manage drug-induced pneumonitis effectively in most settings, such as that seen infrequently with everolimus. However, the DESTINY-Breast01 trial reported a mortality rate of 2.7% due to ILD, with most events occurring during the first year of treatment. One event was noted approximately 20 months after initiation of the infusions. As a result, very careful guidelines were developed on how to manage trastuzumab deruxtecan in patients who have even asymptomatic grade 1 ILD. For example, if chest radiography or computed tomography performed for staging reveals any ground-glass opacities, the T-DXd should be held until the imaging returns to normal, and corticosteroids should be considered. If the patient does not recover within 28 days or the ILD is grade 2 or higher and symptomatic, the drug should be stopped permanently, and patients with grade 2 ILD should be treated with corticosteroids right away. It is hoped that this approach will reduce the number of patients with ILD.

Ongoing studies are evaluating the use of trastuzumab deruxtecan in a variety of settings, as well as in combination with immunotherapy. For example, trastuzumab deruxtecan vs T-DM1 is now being tested in the post-neoadjuvant setting by the German Breast Group and the National Surgical Adjuvant Breast and Bowel Project (NSABP) in the SASCIA trial (NCT04595565). In metastatic disease, T-DXd is being compared with T-DM1 in the second-line setting, and with physician's choice of treatment in later lines. In addition, the phase 3 DESTINY-Breast04 trial, which has completed accrual, is comparing trastuzumab deruxtecan vs physician's choice of treatment in patients who have centrally determined HER2-low disease (NCT03734029), on the basis of encouraging data in this population of patients in a phase 1b expansion trial.

**H&O** Can you describe sacituzumab govitecan in more detail?

**HR** Sacituzumab govitecan received accelerated approval in April 2020 for the treatment of patients with heavily pretreated, metastatic, triple-negative breast cancer, for which few treatment options are available. This drug is an antibody directed to trophoblast cell surface antigen 2 (Trop-2), which is expressed on most breast cancers (among other cancers), regardless of subtype; expression of Trop-2 has been associated with a poor prognosis.

The Trop-2 antibody is linked to the toxin SN-38, a novel metabolite of the topoisomerase I inhibitor irinotecan. As with trastuzumab deruxtecan, the DAR is high, and the drug is given on days 1 and 8 every 3 weeks. An initial expanded phase 1b/2 trial that led to accelerated approval showed a remarkable response rate of more than 30% in patients with refractory triple-negative breast cancer. Results of the phase 3 randomized definitive study, ASCENT, were presented by Bardia and colleagues at the 2020 ESMO Virtual Congress and will soon be published.

The ASCENT trial enrolled 529 patients with metastatic triple-negative breast cancer who had received at least 2 prior chemotherapy regimens for advanced

disease. Patients were randomly assigned to receive either sacituzumab govitecan or physician's choice of treatment, which included eribulin, vinorelbine, gemcitabine, and capecitabine. PFS (the primary endpoint) was significantly longer in the patients receiving sacituzumab than in those receiving physician's choice of treatment: 5.6 vs 1.7 months, a 59% relative improvement. All subgroups of patients benefited, including those who did not have an initial diagnosis of triple-negative breast cancer but whose disease became triple-negative with recurrence. Sacituzumab govitecan also nearly doubled OS compared with physician's choice of treatment, from 6.7 to 12.1 months, with a hazard ratio of 0.48.

ILD in association with treatment was not reported in this study. The most common toxicity was significant neutropenia—51% of patients had grade 3 or higher neutropenia. Other grade 3 or higher toxicities that were more common in the sacituzumab group than in the control group were diarrhea (10% vs <1%), anemia (8% vs 5%), and febrile neutropenia (6% vs 2%). The majority of patients needed short-acting growth factors for the management of neutropenia, but rates of discontinuation owing to toxicity were similar in the 2 arms, at less than 5%. Sacituzumab govitecan is associated with a relatively low rate of nausea when antiemetic premedication is given. Alopecia is frequent with sacituzumab govitecan.

This drug also has shown efficacy in hormone receptor–positive advanced disease, as well as in urothelial cancers. The phase 3 TROPICS-02 trial, which has a design similar to that of ASCENT, has completed accrual (NCT03901339). Data comparing sacituzumab with physician's choice of treatment in hormone receptor–positive disease are expected within the next year.

**H&O** What questions remain to be answered regarding ADCs?

**HR** A number of questions remain. The first pertains to the management of toxicity and its incidence as well as severity in less heavily pretreated patients—particularly ILD. Additional questions pertain to moving these effective novel therapies earlier into the course of treatment. All 3 of the approved drugs are now being studied in combination with immunotherapy, and also in patients with brain metastases.

One of our goals is to move ADCs into the early-stage setting, as described earlier in regard to the SASCIA trial and the study of T-DXd vs T-DM1. Additional ADCs that target Trop-2 are being developed, and an agent that targets HER3 is producing positive early results.

The ADC SYD985, which is being compared with standard therapy in patients who have metastatic HER2-positive disease in the phase 3 TULIP trial (NCT03262935), is a novel trastuzumab-based ADC linked to an alkylating agent, duocarmazine. This ADC demonstrated efficacy in a phase 1b expansion trial; associated toxicities included ocular disease and neutropenia.

**H&O** Are you using all 3 of these agents in your practice?

**HR** Absolutely. We use T-DM1 in the second-line setting and the post-neoadjuvant setting. Trastuzumab deruxtecan is highly effective in metastatic HER2-positive breast cancer but should be avoided in patients with a history of pneumonitis. Sacituzumab govitecan is our treatment of choice for patients with pretreated metastatic triple-negative breast cancer.

## Suggested Readings


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