BREAST CANCER

Groundbreaking ADCs Are Expanding to New Settings for More Patients With Breast Cancer

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MANY PRESENTATIONS FROM the 2022 San Antonio Breast Cancer Symposium (SABCS) looked to further understand and find greater roles for the use of antibody-drug conjugates (ADCs) in breast cancer.

Presenters noted how these ADCs have been changing the treatment landscape for patients with breast cancer, with the focus to expand the clinical impact of these agents into more settings and provide patients with improved outcomes.

"The rationale for developing ADCs was really to try and overcome the limitations of cytotoxic therapies…[thus] improving the therapeutic index," said **Shanu Modi**, **MD**, section head of the HER2 Breast Program at Memorial Sloan Kettering Cancer Center, in a presentation at SABCS.

"Technological advancements have brought us into an exciting era of ADC therapy. These next-generation drugs have improved efficacy, they have broader clinical applicability, and we've expanded the target antigen landscape," she added.

HER2-Directed ADCs

Trastuzumab Emtansine

Ado-trastuzumab emtansine (Kadcyla) was the first ADC approved in breast cancer for the treatment of patients with HER2-positive, metastatic disease. The prototype HER2-directed ADC consists of trastuzumab (Herceptin) linked to a microtubule inhibitor conjugate and a noncleavable thioether linker.

"When [trastuzumab emtansine] was made available clinically, it really was a profoundly important drug and a groundbreaking drug in breast cancer," Modi said. "It [became] our standard of care as second-line therapy for close to a decade."

Trastuzumab emtansine was explored as a possible adjuvant therapy for patients with stage I HER2-positive breast cancer in comparison with adjuvant trastuzumab and paclitaxel in the phase 2 ATEMPT trial (NCT01853748). The majority of patients had HER2 3+ expression by immunohistochemistry (IHC) and had hormone receptor–positive disease.

Findings from an end-of-study analysis of the trial presented in a poster at SABCS showed that at a median follow-up of 5.8 years, the 5-year invasive disease-free survival rate with trastuzumab emtansine was 97.0% (95% CI, 96.2%-98.7%) and the 5-year overall survival (OS) rate was 97.8% (95% CI, 96.3%-99.3%).[1] Comparatively, the 5-year invasive disease-free survival rate with trastuzumab and paclitaxel was 91.3% (95% CI, 86.0%-96.9%) and the 5-year OS rate was 97.9% (95% CI, 95.2%-100%).

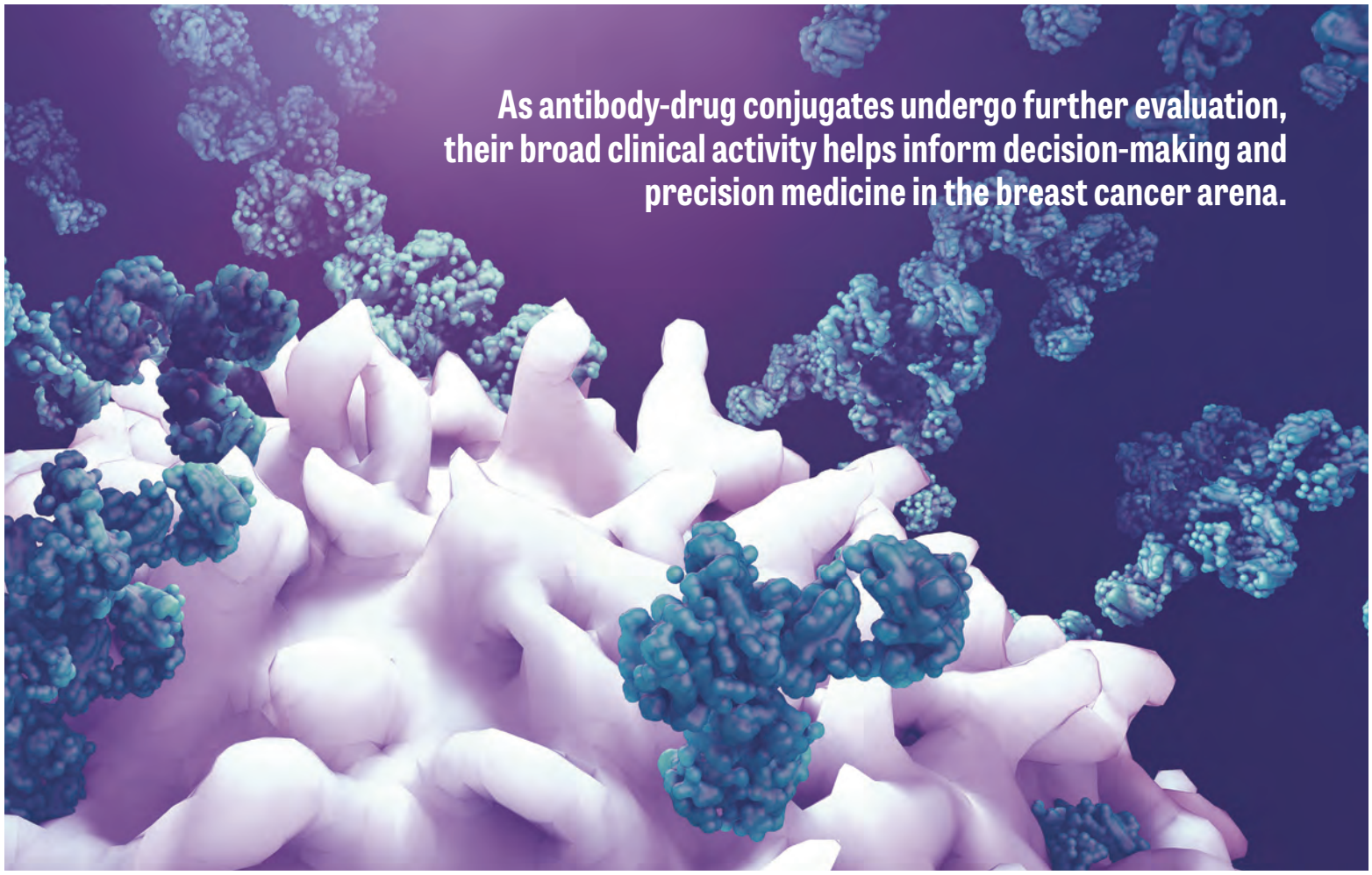
The multicohort phase 2 TBCRC 022 trial (NCT01494662) investigated the use of neratinib (Nerlynx) with trastuzumab emtansine in patients with HER2-positive breast cancer and brain metastases. In cohort 4A (n=6), patients had previously untreated brain metastases; cohort 4B (n=17) had progressive brain metastases and no prior trastuzumab emtansine exposure; and cohort 4C (n=21) had progressive metastases and prior trastuzumab emtansine exposure.[2]

Patients had received a median of 2 prior lines of chemotherapy in the metastatic setting (range, 0-10). In the progressive metastases cohorts, the majority of patients had also received whole brain radiation therapy and/or stereotactic radiosurgery.

The central nervous system objective response rate (ORR) in cohort 4A was 33.3% (95% CI, 4.3%-77.7%), 29.4% (95% CI, 10.3%-56.0%) in cohort 4B, and 28.6% (95% CI, 11.1%-52.2%) in cohort 4C. At 1 year, the OS rates were 83.3% (95% CI, 58.3%-100%), 87.5% (95% CI, 72.7%-100%), and 83.3% (95% CI, 67.6%-100%) in cohorts 4A, 4B, and 4C, respectively.

Trastuzumab Emtansine vs Trastuzumab Deruxtecan

Trastuzumab emtansine was compared with the newer ADC fam-trastuzumab deruxtecan-nxki (Enhertu) in patients with unresectable or metastatic HER2-positive breast cancer who had previously received trastuzumab and a taxane in the metastatic or neoadjuvant/adjuvant setting, with recurrence within 6 months of treatment,



in the phase 3 DESTINY-Breast03 trial (NCT03529110).[3]

Trastuzumab deruxtecan is a next-generation humanized HER2-directed ADC with a higher drug to antibody ratio than trastuzumab emtansine, as well as a high potency of the topoisomerase I (TOP1) inhibitor payload, a tetrapeptide-based cleavable linker, and a bystander antitumor effect.

The majority of patients had HER2 3+ status by IHC, hormone receptor–positive disease, and a history of visceral disease. The median number of prior lines of therapy in the metastatic setting was 2 (range, 0-16).

The median PFS was 28.8 months (95% CI, 22.4-37.9) with trastuzumab deruxtecan compared with 6.8 months (95% CI, 5.6-8.2) with trastuzumab emtansine (HR, 0.33; 95% CI, 0.26-0.43; *P*<.000001). "That's 4 times longer than with [trastuzumab emtansine]; that's pretty spectacular," Modi commented during the presentation. The PFS rates at 2 years were 53.7% (95% CI, 46.8%-60.1%) and 26.4% (95% CI, 20.5%-32.6%) with trastuzumab deruxtecan and trastuzumab emtansine, respectively.

Median OS was not reached in either treatment arm, but showed a trend favoring trastuzumab deruxtecan (HR, 0.64; 95% CI, 0.47-0.87; *P* = .0037). At 2 years, the OS rate with trastuzumab deruxtecan was 77.4% (95% CI, 71.7%-82.1%), and 69.9% (95% CI, 63.7%-75.2%) with trastuzumab emtansine.

The confirmed ORR by blinded independent central review (BICR) was 78.5% (95% CI, 73.1%-83.4%) with trastuzumab deruxtecan vs 35.0% (95% CI, 29.2%-41.1%) with trastuzumab emtansine. Complete responses were observed in 21.1% of the trastuzumab deruxtecan arm and in 9.5% of the trastuzumab emtansine arm. The median duration of response was 36.6 months (95% CI, 22.4-not evaluable [NE]) vs 23.8 months (95% CI, 12.6-34.7) with trastuzumab deruxtecan and trastuzumab emtansine, respectively. "Patients who respond to [trastuzumab deruxtecan] can stay on this therapy for a very long time," Modi noted.

"The results we saw…certainly support [trastuzumab deruxtecan] as the superior HER2 ADC and the preferred second-line therapy for HER2-positive metastatic breast cancer today," she said.

Trastuzumab Deruxtecan

Trastuzumab deruxtecan is approved for use in breast cancer both for patients with HER2-positive disease and those with HER2-low breast cancer, following the results from the DESTINY-Breast04 trial (NCT03734029).

"Overall, [trastuzumab deruxtecan] is a really exciting and versatile new-generation HER2 ADC by virtue of its novel linker-payload technology," Modi said. "It's currently, in my opinion, the most effective HER2-targeted therapy that we have in the clinic. It has allowed us to expand HER2-targeted therapy into new populations and settings."

"We know that dependence on internalization additive effects of a pan-HER2 inhibitor, which increased internalization, seems to be quite prominent for [trastuzumab emtansine] because so much of the effect was related to internalization per se. The contrast was [trastuzumab deruxtecan]

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because of the less stable linker. Even early studies showed that you could see in vitro resistance to [trastuzumab emtansine] mediated by loss of lysosomal integrity, and that resistance could be overcome by [trastuzumab deruxtecan] because it doesn't require an active lysosome to release payload intracellularly. And we don't know for sure, but perhaps that contributes to some of the very exciting data that we saw for the use [of trastuzumab deruxtecan] after [trastuzumab emtansine] in advanced HER2-positive breast cancer," said **Leif W. Ellisen**, **MD**, **PhD**, program director for breast medical oncology at Massachusetts General Hospital Cancer Center in Boston, in a presentation at SABCS.

One of the most significant study results from 2022 SABCS was that of the randomized phase 3 DESTINY-Breast02 trial (NCT03523585), in which trastuzumab deruxtecan led to a significant improvement in progression-free survival (PFS) and OS compared with treatment of physician's choice (TPC) among patients with advanced HER2-positive unresectable and/or metastatic breast cancer who previously received trastuzumab emtansine.[4]

Patients had received a median of 2 (range, 0-10) prior lines of therapy. These included prior trastuzumab and trastuzumab emtansine in 100% of patients, a taxane in 96%, pertuzumab (Perjeta) in 78%, and hormonal therapy in 73%.

The median PFS with trastuzumab deruxtecan (n=406) was 17.8 months (95% CI, 14.3-20.8) compared with 6.9 months (95% CI, 5.5-8.4) with TPC (n=202; HR, 0.3589; 95% CI, 0.2840-0.4535; *P*<.000001). At 24 months, the PFS rates were 42.2% and 13.9% with trastuzumab deruxtecan and TPC, respectively.

Median OS was 39.2 months (95% CI, 32.7-NE) with trastuzumab deruxtecan vs 26.5 months (95% CI, 21.0-NE) with TPC (HR, 0.6575; 95% CI, 0.5023-0.8605; *P*=.0021). The OS rate at 2 years was 65.9% with trastuzumab deruxtecan and 54.3% with TPC.

The ORR by BICR was 69.7% (95% CI, 65.0%-74.1%) with trastuzumab deruxtecan compared with 29.2% (95% CI, 23.0%-36.0%) with TPC (*P*<.0001).

"Overall, the results of DESTINY-Breast02, I think, are really compelling, and suggest that not only is [trastuzumab deruxtecan] more effective than our standard chemotherapy approach, but it also is proved to be active post [trastuzumab emtansine]," Modi said.

The ADC is also being studied in earlier settings. In the phase 2 TRIO-US B-12 TALENT trial (NCT04553770), trastuzumab deruxtecan was investigated in the neoadjuvant setting with or without anastrozole in patients with hormone receptor–positive, HER2-low, early-stage breast cancer.[5]

Patients had stage II or III operable disease and were randomly assigned to receive trastuzumab deruxtecan treatment with or without anastrozole for 6 or 8 cycles, as the number of cycles was increased partway through the study. About half the patients had node-positive disease, and most patients had invasive ductal histology.

In the monotherapy arm (n=25), the ORR was 68%, including complete responses in 8% of patients. With added anastrozole (n=24), the ORR was 58% and complete responses were seen in 8% of patients. Changes in HER2 IHC were also noted after treatment with trastuzumab deruxtecan in 49% of patients, accounting for a decrease in expression for 88% of these patients.

"I do think that the trial [data are] instructive in showing us that we can safely deliver 6 to 8 cycles of [trastuzumab deruxtecan] in the neoadjuvant setting, and there's certainly a tremendous wealth of translational research that will allow us to better understand the mechanics of [the agent]," Modi commented.

Synergy with trastuzumab deruxtecan is also being explored with other systemic therapies, including with further HER2-targeted therapy and immunotherapy.

In the ongoing DESTINY-Breast07 study (NCT04538742), trastuzumab deruxtecan is being explored as a monotherapy and in various combination regimens in patients with advanced and unresectable or metastatic HER2-positive breast cancer.[6]

When studied in combination with pertuzumab, the regimen led to an ORR of 81.8%

TABLE. Outcomes With Trastuzumab Deruxtecan Monotherapy Across Trials

TRIAL	COMPARATOR	DISEASE SETTING	NUMBER OF PATIENTS	PFS	OS	ORR	DOR	REFERENCE
DESTINY-Breast01 (NCT03248492)		HER2+ metastatic breast cancer, prior trastuzumab emtansine	184	19.4 months	29.1 months	62.0%	18.2 months	13
DESTINY-Breast02 (NCT03523585)	Treatment of physician's choice	HER2+ unresectable or metastatic breast cancer, prior trastuzumab emtansine, progression after last treatment	406	17.8	39.2 months	69.7%	19.6 months	4
DESTINY-Breast03 (NCT03529110)	Trastuzumab emtansine	HER2+ unresectable or metastatic breast cancer, prior trastuzumab and taxane in metastatic or neoadjuvant/adjuvant setting, recurrence within 6 months	261	28.8 months	NR	78.5%	36.6 months	3
DESTINY-Breast04 (NCT03734029)	Treatment of physician's choice	HER2-low metastatic breast cancer, 1-2 prior lines of chemotherapy	557	9.9 months	23.4 months	52.3%	10.7 months	14
DESTINY-Breast07 (NCT04538742)		HER2+ metastatic breast cancer, no prior therapy for advanced/metastatic disease	23	—	—	87.0%	—	6
TRIO-US B-12 TALENT (NCT04553770)	Trastuzumab deruxtecan with anastrozole	HR+, HER2-low, stage II-III operable breast cancer	22	—	—	68.0%	—	5

DOR, duration of response; HR, hormone receptor; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

(95% CI, 66.9%-91.8%), with confirmed responses in 72.7% of patients (95% CI, 57.0%-85.0%). All responses were partial.

The combination is being explored further in an arm in the ongoing DESTINY-Breast09 study (NCT04784715). "All eyes are now on DESTINY-Breast09," Modi noted, adding that this is potentially a practice-changing trial.

Trastuzumab deruxtecan is also being investigated in combination with durvalumab (Imfinzi) in the phase 1b/2 BEGONIA platform study (NCT03742102) in patients with unresectable locally advanced or metastatic hormone receptor–negative, HER2-low breast cancer.[7]

Updated results from the study presented at SABCS 2022 showed a confirmed ORR of 56.9% (95% CI, 43.2%-69.8%), including 1 complete response. The median PFS was 12.6 months (95% CI, 8.3-not calculated). By HER2 expression, the ORR was 67.6% (95% CI, 50.2%-82.0%) for those with 1+ expression by IHC, and 38.1% (95% CI, 18.1%-61.6%) for those with IHC 2+/in situ hybridization–negative expression.

TROP-2–Directed ADCs

Sacituzumab Govitecan

Sacituzumab govitecan-hziy (Trodelvy) is a first-in-class Trop-2–directed ADC that is approved for the treatment of patients with unresectable locally advanced or metastatic triple-negative breast cancer who have received 2 or more prior systemic therapies, including at least 1 for metastatic disease. Trop-2 is highly expressed in approximately 85% to 90% of all breast cancer subtypes and also is associated with a poor prognosis.

Sacituzumab govitecan consists of a humanized anti–Trop-2 antibody, an SN-38 payload, and a hydrolysable carbonate linker. The ADC has a high drug to antibody ratio, and hydrolysis of the linker releases cytotoxic SN-38 extracellularly.

Ellisen noted that sacituzumab govitecan, unlike trastuzumab emtansine, has a greater bystander effect. "[Sacituzumab govitecan,] with its relatively unique unstable linker where you get all of this microenvironmental release, [has] both pros and cons, perhaps with great tumor heterogeneity that could overcome some of the resistance because of the extensive extracellular, intracellular bystander effect, but on the other hand may relate to other toxicities, such as myelotoxicities, from the payload being released," he said.

Ongoing studies are looking to move the ADC into other subtypes where it can be beneficial. In the phase 3 TROPiCS-02 trial (NCT03901339), sacituzumab govitecan was explored in patients with pretreated, endocrine-resistant, hormone receptor–positive, HER2-negative metastatic breast cancer in comparison with TPC.

> **"[Trastuzumab deruxtecan is] currently, in my opinion, the most effective HER2-targeted therapy that we have in the clinic. It has allowed us to expand HER2-targeted therapy into new populations and settings."**
>
> **– SHANU MODI, MD**

The majority of patients had an ECOG performance status of 1 and visceral metastasis. They also had received 3 or 4 prior chemotherapy regimens for metastatic disease and CDK4/6 inhibition within 12 months.

Findings from the first interim analysis showed that the median PFS was 5.5 months with sacituzumab govitecan (n= 272) compared with 4.0 months with TPC (n=271; HR, 0.66; 95% CI, 0.53-0.83; *P*=.0003).[8] As of the second interim analysis data, the median OS in the overall population was 14.4 months with sacituzumab govitecan vs 11.2 months with TPC (HR, 0.79; 95% CI, 0.65-0.96; *P*=.02). The ORR was 21% with the ADC and 14% with TPC (odds ratio, 1.63; 95% CI, 1.03-2.56; *P*=.035).[9]

"This study has hit both its primary and secondary end points, and the [National Comprehensive Cancer Network] has already endorsed sacituzumab [govitecan] as an option for [patients with] hormone [receptor]-positive, HER2-negative metastatic breast cancer while we await regulatory approval," Modi said.

At SABCS 2022, investigators presented findings showing that sacituzumab govitecan benefited patients in this setting regardless of their level of Trop-2 expression. Median OS in patients with a Trop-2 expression score of 100 or more was 14.4 months (95% CI, 12.7-16.4) with sacituzumab govitecan and 11.2 months (95% CI, 9.9-12.9) with TPC (HR, 0.83; 95% CI, 0.62-1.11). Patients with a score below 100 had a median OS of 14.6 months (95% CI, 12.7-18.1) with the ADC and 11.3 months (95% CI, 10.0-13.3) with standard therapy (HR, 0.75; 95% CI, 0.54-1.04).[10]

More specifically, among patients with a score of 10 or lower, the median OS was 17.6 months (95% CI, 11.5-NE) with sacituzumab govitecan compared with 12.3 months (95% CI, 8.0-15.3) with TPC (HR, 0.61; 95% CI, 0.34-1.08). For those with a score between 10 and 100, the median OS was 13.7 months (95% CI, 10.9-16.3) and 11.0 months (95% CI, 9.0-13.5), respectively (HR, 0.81; 95% CI, 0.54-1.23).

Datopotamab Deruxtecan

Datopotamab deruxtecan is an investigational, differentiated Trop-2–directed ADC comprising a humanized anti–Trop-2 IgG1 monoclonal antibody, a TOP1 inhibitor payload, and a tetrapeptide-based cleavable linker. The ADC has a high potency of payload, a stable linker-payload, a tumor-selective cleavable linker, and a resulting bystander antitumor effect.

In the dose-escalation and dose-expansion phase 1 TROPION-PanTumor01 trial (NCT03401385), datopotamab deruxtecan was investigated in patients with advanced or metastatic solid tumors. Among patients with advanced triple-negative breast cancer, most did not have de novo metastatic disease but did have an ECOG performance status of 1. The median number of prior therapies in the metastatic setting was 3 (range, 1-10), including taxanes in 93% of patients, anthracyclines in 75%, and capecitabine in 61%.[11]

The median PFS by BICR was 4.4 months (95% CI, 3.0-7.3) with datopotamab deruxtecan. Among patients without any exposure to TOP1 inhibition, the median PFS was 7.3 months (95% CI, 3.0-18.0). The median OS was 13.5 months (95% CI, 10.1-16.3) in the overall population, and 14.3 months (95% CI, 10.5-NE) in the TOP1 inhibitor–naïve patients.

In another arm of the BEGONIA study, durvalumab was combined with datopotamab deruxtecan in patients with unresectable

locally advanced or metastatic triple-negative breast cancer. Only 41% of patients had no prior treatment, as most others had received radiotherapy or chemotherapy. The majority of patients also had visceral metastases, lymph node metastases, and low PD-L1 expression.[12]

The confirmed ORR was 73.6% (95% CI, 59.7%-84.7%), including complete responses in 7.5% of patients. The unconfirmed ORR was 80.0% (95% CI, 67.7%-89.2%). Longer follow-up is needed to determine PFS.

"We'll definitely see these combinations move forward," Modi commented.

Next Steps, Ongoing Challenges With ADCs

Going forward, Modi noted that "a clinically critical and emerging…problem for clinicians is how do we best select and sequence these ADC therapies," as there are overlaps in populations that can receive multiple ADCs. Ellisen agreed that sequential use of multiple ADCs can likely be effective in informed settings.

Modi added that clinicians could benefit from novel predictive biomarkers of response and comparative studies. "Fundamentally, we need a greater understanding of the mechanisms of resistance. This will allow us to really advance the field," she said, and allow for more personalized treatment choices.

"The systematic analysis of distinct mechanisms coupled with analysis of patient material will accelerate development and indeed be essential for new ADCs and combinations to prevent and overcome resistance," Ellisen added.

"With all of the tools available to us today, as clinicians, we are really relying on cross-trial comparisons and safety cross-trial comparisons to guide our treatments. So, if we come back to the clinical dilemma that we all face today—what do we do with that [patient with] HER2-negative metastatic breast cancer who is eligible for both ADCs?" Modi asked in her presentation at SABCS. "I think one approach is to look at the HER2 status, particularly for the [hormone receptor]–positive, HER2-negative patients if they have an IHC of 1+ or 2+, they would be candidates for trastuzumab deruxtecan based on DESTINY-[Breast04 data]. For those with an IHC score of 0, [treatment would be] sacituzumab govitecan based on [findings from] TROPiCS-02. And of course, for those patients with… triple-negative breast cancer, while there [are]compelling data in DESTINY-[Breast0]4 for activity of [trastuzumab deruxtecan] in HER2-low, hormone receptor–negative breast cancer, I think if we look at the wealth of the data—and the level 1 data [are] from the sacituzumab [govitecan] arena, and I think this would be an appropriate option for this setting." **TT**

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