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# Evolving HER2+ Metastatic Breast Cancer Landscape

**H**ER2-positive metastatic breast cancer has historically been considered a difficult-to-treat disease given that it is often more aggressive than other breast cancers. However, several recently established targeted treatment options that prolong survival and enhance quality of life now offer hope to patients and their care providers. And although these advancements are of great benefit to both patients and their treating clinicians, questions about choosing the appropriate therapy and sequencing different lines of treatment remain.

Four experts reviewed these new developments in an online discussion as part of an *Around the Practice* event hosted by CancerNetwork®, moderated by **Andrew D. Seidman, MD**, an attending physician for the breast medicine service at Memorial Sloan Kettering Cancer Center, who covered the current standard of care as well as novel and emerging therapies. The other panelists were **Aditya Bardia, MD, MPH**, a breast medical oncologist at Massachusetts General Hospital and assistant professor of

medicine at Harvard Medical School in Boston, Massachusetts; **Mark Pegram, MD**, a professor of medical oncology at the Stanford University School of Medicine in California; and **Ruta Rao, MD**, who is associate professor in the Department of Internal Medicine, Division of Hematology, Oncology, and Cell Therapy at Rush Medical College; director, Coleman Foundation Comprehensive Breast Cancer Clinic; and medical director, Rush University Cancer Center, all in Chicago, Illinois. The discussion also included audience polls, which the speakers discussed as part of their program.

## **A Rapidly Changing Therapeutic Landscape**

The discussion began with a review of current options for first- and second-line therapy in the treatment of HER2-positive metastatic breast cancer. Pegram, who runs a research lab focused on targeted therapies for HER2-positive disease, discussed the regimen consisting of trastuzumab (Herceptin) and pertuzumab (Perjeta) combined with taxane chemotherapy,

usually paclitaxel. Oncologists favor this regimen because of the highly successful randomized double-blind phase 3 CLEOPATRA trial (NCT00567190), the updated results of which indicated that patients assigned to the active regimen had a median overall survival (OS) that was 16.3 months longer than that of patients assigned to placebo (HR, 0.69; 95% CI, 0.58-0.82).<sup>1</sup>

“That’s a huge survival benefit that has been persistent over the 8 years since that trial [was] first reported,” said Pegram. “Very impressive results and so far, nothing has been able to dethrone the CLEOPATRA regimen in the first-line setting.”

An established second-line treatment, trastuzumab emtansine (Kadcyla; TDM-1), has been recommended by guidelines and put into standard practice since the publication of the EMILIA trial (NCT00829166) in 2012,<sup>3</sup> Pegram added. In a 2017 update, patients assigned to the study regimen experienced a superior survival benefit compared with controls assigned to capecitabine plus lapatinib (Tykerb).<sup>4</sup>

However, the results of an upcoming trial may displace the generally accepted CLEOPATRA regimen in the frontline setting, according to Pegram. In the DESTINY-Breast 09 study (NCT04784715), investigators will compare a regimen consisting of trastuzumab deruxtecan (Enhertu; T-DXd) with or without pertuzumab with a control group assigned to the CLEOPATRA-style routine.

The TDM-1 regimen is also being challenged in the second line. Investigators recently reported findings from the phase 3 DESTINY-Breast 03 trial (NCT03529110) of T-DXd vs T-DM1 that could change the standard for HER2-positive metastatic breast cancer in this setting.<sup>5</sup>

What’s more, patients with early HER2-positive breast cancer are already being treated with the dual-antibody pairing of trastuzumab

and pertuzumab, and if these patients do not achieve a complete pathologic response, care providers may also administer postneoadjuvant TDM-1.<sup>6</sup>

“The landscape is changing,” Pegram said. “This concept of lines of therapy now is being blurred, and necessarily, we’ll probably need to shift the definition of lines to the left in the metastatic disease setting as we use all of those agents in the early-disease setting in the future.”

### Survival Outcomes in Recent Clinical Trials

Several trials in recent years have changed the way oncologists care for patients with metastatic HER2-positive breast cancer, and some ongoing trials may improve treatment in the near future.

In CLEOPATRA, investigators randomly assigned a total of 808 patients in a 1:1 fashion to chemotherapy and trastuzumab plus either pertuzumab or placebo. The primary end point was progression-free survival (PFS) as determined by independent review; secondary outcomes included OS, PFS as determined by investigators, objective response rate, duration of objective response, and time to disease progression. The investigators found that the pertuzumab combination greatly extended median PFS (HR, 0.69; 95% CI, 0.58-0.81) and subsequently was found to have a dramatic benefit to OS, as Pegram mentioned at the beginning of the program.<sup>2</sup>

In the phase 3 KATHERINE (NCT01772472) trial, investigators assigned 1486 patients to either adjuvant trastuzumab or trastuzumab emtansine following surgery. The main outcome was invasive disease-free survival, with patients in the TDM-1 group demonstrating a 50% lower risk of recurrence of invasive breast cancer or death than those assigned to trastuzumab alone (HR, 0.50; 95% CI, 0.39-0.64;  $P < .001$ ).<sup>7</sup>

In EMILIA, the efficacy of trastuzumab emtansine was compared with that of capecitabine and lapatinib; investigators randomly assigned 991 patients with previously treated, advanced disease to receive either therapy. The main outcome measures were PFS, OS, and safety. Trastuzumab emtansine was found to significantly improve PFS, and it lowered overall toxicity compared with capecitabine and lapatinib at the first analysis (HR, 0.65; 95% CI, 0.55-0.77;  $P < .001$ ), with the final descriptive analysis revealing a 25% reduction in the risk of disease progression or death (HR, 0.75; 95% CI, 0.64-0.88).<sup>3,4</sup>

The 2021 American Society of Clinical Oncology meeting saw the presentation of updated results from the pivotal phase 3 HER2CLIMB study (NCT02614794) that randomized 612 patients with unresectable metastatic or locally advanced HER2-positive breast cancer in a 2:1 fashion to receive either trastuzumab and capecitabine alone or in combination with tucatinib (Tukysa). Investigators reported a survival benefit in the tucatinib group 15.6 months following the primary analysis, with patients assigned to tucatinib experiencing a 5.5-month improvement in OS compared with the placebo group (HR, 0.73; 95% CI, 0.59-0.90;  $P = .004$ ).<sup>8</sup>

Data from DESTINY-Breast03 in 524 patients randomly assigned to T-DXd vs T-DM1 that were presented at the European Society for Medical Oncology 2021 Congress indicated that the median PFS was not reached in the trastuzumab deruxtecan group compared with 6.8 months in the T-DM1 group (HR, 0.28; 95% CI, 0.22-0.37;  $P = 7.8 \times 10^{-22}$ ). Patients assigned to trastuzumab deruxtecan were also treated longer, at a median of 14.3 months compared with 6.9 months for those assigned to T-DM1. Both groups showed similar safety profiles of the agents.<sup>5</sup>

The NALA trial (NCT01808573),

a global, open-label phase 3 study of 621 patients with previously treated HER2-positive breast cancer, which included 3 men and compared survival with capecitabine plus either neratinib (Nerlynx) or lapatinib was discussed by Seidman. The study also included patients with stable, asymptomatic central nervous system (CNS) disease. The main outcomes were PFS and OS as determined by a blinded review, with

statistically significant improvements in both end points noted in 2020. The HR for progression or death was 0.76 (95% CI, 0.63-0.93; stratified log-rank  $P = .0059$ ), and for survival the HR was 0.88 (95% CI, 0.72-1.07;  $P = .2098$ ). A 2021 update found that the neratinib combination outperformed lapatinib in terms of both PFS (7.8 vs 5.5 months; HR, 0.66; 95% CI, 0.41-1.05;  $P = .0741$ ) and OS (16.4

vs 15.4 months; HR, 0.90; 95% CI, 0.59-1.38;  $P = .6352$ ) in a subgroup of patients with CNS involvement.<sup>9,10</sup>

### Metastatic HER2-Positive Disease in Patient Cases

After a discussion of these data for approved therapies to treat HER2-positive breast cancer, the panel turned to a series of case studies regarding third-line treatment options.

#### Case 1

- A woman, aged 57 years, presented with a 1.8-cm left breast mass and 3 palpable axillary lymph nodes.
- Medical history: significant for chronic obstructive pulmonary disorder; a 20 pack-year history of smoking; active smoker
- Baseline pulmonary function tests: mildly impaired diffusing capacity of lungs for CO<sub>2</sub> (83%)
- Biopsy: invasive ductal carcinoma; estrogen receptor–negative/progesterone receptor–negative; HER2 by immunohistochemistry testing, 3+
- CT of chest/abdomen/pelvis (CAP): 2 lung lesions (largest 1.6 cm)
- MRI of the brain: negative for metastasis
- The patient received 6 cycles of trastuzumab plus pertuzumab (HP) and taxane chemotherapy (THP), followed by HP alone. A partial response was observed in breast mass, as was a complete response in lung lesions.
- Ten months later, recurrence in 2 lung lesions were discovered (largest 0.9 cm).
- The patient received T-DXd with a partial response observed in both the breast and lung lesions.
- Eighteen months later, growth of 1 lung lesion and a new 1.2-cm liver metastasis were noted on CT CAP.

When polled about how they would treat a patient whose disease had progressed to the lung and liver after earlier treatments had cleared previous metastases, 50% of all audience members responded that they would use the HER2CLIMB regimen of tucatinib plus trastuzumab and capecitabine, making that regimen the most popular choice in the poll.

“I can say that there’s definitely more

than 1 right answer. In the metastatic setting, we use therapy sequentially, so it’s about choosing 1 therapy [first],” Bardia said. “Then in the future, you’d be using other regimens. I’m not that surprised [by this response], given the excitement around HER2CLIMB. There’s a lot of interest in utilizing tucatinib, and maybe that is what prompted the use of trastuzumab, capecitabine, and tucatinib.”

Another popular response was

T-DM1. “It’s very well tolerated and I think it is an agent that should be used in the metastatic setting. I’d personally either consider TDM-1 or tucatinib,” Bardia added.

Seidman then guided the conversation to a discussion of treatment options for a woman, aged 35 years, who “indicates that her main priority is to live as normally as possible,” without nausea or diarrhea.

#### Case 2

- A woman, aged 35 years, with hormone receptor–negative, HER2-positive metastatic breast cancer, presented in the clinic.
- She completed first-line therapy with THP and then progressed while on maintenance HP.
- At that time, she was treated with T-DXd.
- Twenty months later, she has low-volume asymptomatic bone metastases.
- She has 2 children and says that her main priority is to live as normal a life as possible while being treated. She wants to spend her weekends at the soccer fields and doesn’t want to have nausea or diarrhea, AEs that would make that difficult.

At this point, Rao said it would be important to discuss adverse effect (AE) profiles of each available agent with the patient.

“In this particular case, if she’s telling you she doesn’t want to have nausea or diarrhea and you’re talking to her about the different options and the different AEs associated with each, you’re going to tell her about the rates of diarrhea and nausea seen with the HER2CLIMB regimen,” Rao said. “It’s really important to have that discussion with the patient about how we don’t know which of the 2 third-line treatment options is superior because they have not been compared head-to-head. But if you look at the AEs each one has and the desires the patient has, that will help make a decision.”

Pegram added that the patient could be given an antidiarrheal medicine as needed. “For tucatinib, It’s fine to use it as needed,” said Pegram. “They don’t need it prophylactically [since] the incidence of diarrhea isn’t that high. For T-DXd, they don’t need prophylactic antidiarrheal regimens either. The one case where you absolutely must use prophylactic treatment is the case of neratinib.”

Pegram also said that CNS metastases could play a major role in selecting a therapy. In particular, he said, the HER2CLIMB regimen would be an obvious choice for dealing with brain lesions.

“We now have level 1 evidence from a randomized phase 3 trial of an OS benefit of tucatinib-based treatment with the HER2-CLIMB regimen, specifically for HER2-positive CNS metastasis,”<sup>11</sup> said Pegram. “Moreover, the FDA label language for the approval of tucatinib specifically calls out those patients with HER2-positive breast cancer brain metastases.<sup>12</sup> [These] are patients of particular interest for the tucatinib-based treatment.”

## Sequencing of Therapies

A final poll question asked audience

members when they would use the most active regimens available to treat their patients. The response, Seidman noted, was unanimous: All participants responded that they would use the most active regimen available as early as possible. “We’ve got a strong preference to lead with your best foot,” he said.

The panelists had several reasons for leading with the most active therapy. “Both from the CLEOPATRA trial—with the significant improvement in OS—and even in the DESTINY-Breast03 trial, we’ve seen a significant improvement in PFS, [meaning] that these patients can do well for a long time, especially when we give them our most active regimens first,” Rao said.

Pegram noted that patients often tend to drop out of treatment as they move through lines of therapy, which could mean that they may never reach third-line therapy.

“If you’re going to save your best drug for a rainy day, that rainy day may never come because the patient may get too sick from their underlying disease to ever have the opportunity to take the best treatment available,” Pegram said. “That’s another reason why it’s wise to use your best drugs first.”

The panel ended with an acknowledgment of the great strides made in treating HER-positive metastatic breast cancer in recent years. Seidman concluded, “Some people have said that we have an embarrassment of riches in HER2-positive metastatic breast cancer, but we all still have patients who are [dying] from advanced HER2-positive breast cancer. As much progress as we’ve made, we still have quite a way to go—but we certainly have reasons for optimism.” ■

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