BREAST CANCER IN FOCUS

Current Developments in the Management of Breast Cancer

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Optimal Treatment for Metastatic HER2+ Breast Cancer

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H&O How common is human epidermal growth factor receptor 2 (HER2) overexpression in metastatic breast cancer?

ST Approximately 15% to 20% of all breast cancers are HER2-positive. We are curing more cases of early-stage disease that is HER2-positive, so the chance that these patients will experience recurrence with metastatic disease has been reduced. As a result, an increasing proportion of patients who present with metastatic HER2-positive breast cancer are those with de novo metastatic disease.

H&O What is the current standard first-line therapy for metastatic HER2-positive breast cancer?

ST Over the past decade, the standard treatment in the first-line setting has been the CLEOPATRA regimen,[1] which consists of a taxane plus dual HER2-directed therapy with trastuzumab and pertuzumab. This regimen usually comprises an induction phase with a taxane, trastuzumab, and pertuzumab (T), followed by a maintenance phase with trastuzumab and pertuzumab (HP). Although it has long been the standard, the paradigm is evolving on the basis of data from several phase 3 trials, including DESTINY-Breast09,[2] PATINA,[3] and HER2CLIMB-05.[4]

The DESTINY-Breast09 trial compared trastuzumab deruxtecan, also known as T-DXd (Enhertu, Daiichi-Sankyo/AstraZeneca) with or without pertuzumab vs THP in the first-line setting. The study demonstrated that the median progression-free survival (PFS) was significantly longer with T-DXd and pertuzumab than with THP, at 40.7 vs 26.9 months, respectively. These findings led to US Food and Drug Administration (FDA) approval of this combination on December 15, 2025.

The PATINA trial, which examined patients who had estrogen receptor (ER)–positive, HER2-positive disease, focused on optimizing the maintenance phase of the CLEOPATRA regimen. In PATINA, patients who had received induction chemotherapy plus HP were randomly assigned to either endocrine therapy and HP or endocrine therapy and HP plus the CDK4/6 inhibitor palbociclib (Ibrance, Pfizer); the study showed a substantial improvement in PFS with the addition of palbociclib. I hope that this finding will lead to FDA approval for endocrine therapy and HP plus palbociclib as well, so this space is quite dynamic.

More recently, Dr Erika Hamilton presented results from the HER2CLIMB-05 trial at the 2025 San Antonio Breast Cancer Symposium. The patients in this trial, who had HER2-positive metastatic breast cancer and had completed induction chemotherapy, were randomly assigned to first-line maintenance treatment with tucatinib (Tukysa, Seagen) plus HP or placebo plus HP. The researchers found that at a median follow-up of 23 months, the addition of tucatinib to HP improved median PFS from 16.3 to 24.9 months. So as you can see, lots of different strategies are being explored in the first-line setting.

H&O What second-line treatment options are available?

ST The standard second-line treatment in recent years has been T-DXd, on the basis of results from the DESTINY-Breast03 study showing that median PFS was 4 times as long with T-DXd as with trastuzumab emtansine, also known as T-DM1 (Kadcyla, Genentech), at 28.8 vs 6.8 months, respectively.[5] The challenge will be what second-

line treatment to choose if T-DXd is given as first-line treatment: do we select the HER2CLIMB regimen with capecitabine, trastuzumab, and tucatinib, or do we use T-DM1 or even THP?

H&O What approaches are used in the third line and later?

ST The choices depend on what we used in the second line, but T-DM1 is an option if we have not used it yet. If we have not used tucatinib yet, that would be another option. If we do not have those as options, we start shifting toward the use of chemotherapy and trastuzumab or chemotherapy and margetuximab (Margenza, MacroGenics) in later-line settings.

> We have data to suggest that endocrine therapy is still important in HER2-positive disease.

H&O Which patients benefit from continuing anti-HER2 therapy beyond progression?

ST We try to leave all patients with HER2-positive breast cancer on some form of HER2-directed therapy with each of their treatments. We do not want to abandon the HER2-targeting approach; we always want to keep one of these agents on board with each line of therapy.

H&O What strategies are used to reduce resistance to treatment?

ST We are still trying to figure out what is inducing resistance in these patients. For example, when we analyze samples that we have collected, we see a decrease in the level of HER2 expression at the time of progression in approximately two-thirds of patients who have received T-DXd. This finding leads us to wonder if we can use novel approaches to try to enhance HER2 expression. Some data suggest that tucatinib can enhance HER2 expression, which might lead us to think about using tucatinib-based therapy after T-DXd. Another approach would be to use novel combinations of agents. A phase 2 study is looking at use of the experimental antibody-drug conjugate (ADC) disitamab vedotin, which has a monomethyl auristatin E payload, in the post–T-DXd setting to try to overcome payload resistance (NCT06966453). Additional research is looking at a combination of disitamab vedotin and tucatinib to enhance HER2 expression after T-DXd (NCT06157892). Multiple strategies are being considered to help overcome some of these resistance mechanisms.

H&O How do you personalize treatment according to hormone receptor status?

ST We have data to suggest that endocrine therapy is still important in HER2-positive disease. For example, the phase 2 PERTAIN study showed that the addition of pertuzumab to an aromatase inhibitor and trastuzumab led to significant improvements in PFS among patients with HER2-positive, hormone receptor–positive metastatic or locally advanced breast cancer.[6] As a result, when someone with ER-positive disease has received induction therapy with a taxane plus HP, we add endocrine therapy to the HP treatment. We can also consider adding palbociclib to that backbone.

Another drug class that is being studied in HER2-positive, hormone receptor–positive breast cancer is oral selective estrogen receptor degraders. The heredERA registration trial is looking at the addition of giredestrant to trastuzumab and pertuzumab in the maintenance setting (NCT05296798). We are trying to take advantage of hormone receptor status to enhance outcomes.

H&O How do brain metastases influence your treatment decisions?

ST Brain metastases will develop in somewhere between 40% and 50% of all patients with HER2-positive breast cancer in their lifetime, so this is a prevalent problem. When brain metastases are present, we take a different approach to treatment decisions. Patients who have just a few central nervous system (CNS) metastases are good candidates for stereotactic radiation. We can use whole-brain radiation when stereotactic radiation is not feasible because patients have more numerous lesions, but I generally avoid whole-brain radiation in favor of systemic treatment. Fortunately, we have data showing that at least 2 treatment regimens have robust activity in the CNS. In DESTINY-Breast12, the intracranial response rate to T-DXd was approximately 70% in the intention-to-treat group.[7] We also know that tucatinib plus capecitabine and trastuzumab improves survival in patients who have CNS disease, so this combination is another highly effective treatment option that can help us avoid whole-brain radiation. As I decide on the best treatment recommendations for my patients, I usually work with my multidisciplinary colleagues to determine the optimal approach for each patient.

H&O How do you manage toxicities such as interstitial lung disease (ILD)?

ST ILD occurs in approximately 10% to 12% of patients receiving T-DXd, so it is important to monitor patients for this potential adverse event. If grade 1 ILD develops, meaning that the patient is asymptomatic but ground-glass findings are observed on radiographic imaging, we usually hold T-DXd, and I often initiate corticosteroid therapy. If the condition has resolved in 3 to 4 weeks when we repeat imaging, we restart treatment. We generally restart with a dose reduction if the ILD took longer than 28 days to resolve, and we restart at the full dose if the ILD took less than 28 days to resolve. If the ILD is grade 2 or higher (ie, symptomatic), however, we need to discontinue the T-DXd permanently and administer corticosteroids.

H&O What emerging therapies are you most excited about?

ST Many promising drugs are in development for metastatic HER2-positive breast cancer, including the ADCs disitamab vedotin, which I mentioned earlier; ARX788; patritumab deruxtecan (also known as HER3-DXd); SHR-A1811; and trastuzumab botidotin (also known as A166). The phase 3 ACE-Breast-02 trial found that ARX788, which has a monomethyl auristatin F payload, improved survival vs lapatinib plus capecitabine in HER2-positive breast cancer.[8] The phase 1b/2 HERTHENA-Breast-01 study is evaluating patritumab deruxtecan in various combinations for nonresectable HER2-positive breast cancer: with trastuzumab, with trastuzumab and pertuzumab, and with tucatinib and trastuzumab (NCT06686394). The phase 3 HORIZON-Breast01 study found that median PFS was longer with SHR-A1811 than with the pan-HER tyrosine kinase inhibitor pyrotinib plus capecitabine.[9] A phase 3 trial found that median PFS was significantly longer with trastuzumab botidotin than with T-DM1 in patients who had previously treated HER2-positive breast cancer.[10]

Several bispecific antibodies are also being studied for use in breast cancer, including zanidatamab (Ziihera, Jazz Pharmaceuticals), which targets 2 different epitopes on HER2. The phase 3 EmpowHER-303 study is comparing zanidatamab with chemotherapy vs chemotherapy plus trastuzumab in patients whose disease has progressed on T-DXd (NCT06435429).

This treatment space is shifting very quickly, with outcomes that keep getting better. An important question to answer in the coming years is how to sequence treatment optimally.

Disclosures

Dr Tolaney has served in a consulting or advisory role to Novartis, Pfizer/Seagen, Merck, Lilly, AstraZeneca, Genentech/Roche, Eisai, Bristol Myers Squibb/SystImmune, Daiichi Sankyo, Gilead, Blueprint Medicines, Reveal Genomics, Sumitovant Biopharma, Artios Pharma, Menarini/Stemline, Aadi Bioscience, Bayer, Jazz Pharmaceuticals, Natera, Tango Therapeutics, eFFECTOR Therapeutics, Hengrui USA, Cullinan Oncology, Circle Pharma, Arvinas, BioNTech, Launch Therapeutics, Zuellig Pharma, Johnson & Johnson/Ambrx, Bicycle Therapeutics, BeOne Medicines, Mersana Therapeutics, Summit Therapeutics, Avenzo Therapeutics, Aktis Oncology, Boehringer Ingelheim, Celcuity, Samsung Bioepis, Olema Pharmaceuticals, and Tempus; has received research funding from Genentech/Roche, Merck, Exelixis, Pfizer/Seagen, Lilly, Novartis, Bristol Myers Squibb, AstraZeneca, NanoString Technologies, Gilead, OncoPep, Daiichi Sankyo, Menarini/Stemline, and Jazz Pharmaceuticals; and has received travel reimbursement from Lilly, Gilead, Jazz, Pfizer, Arvinas, Roche, and AstraZeneca.

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