For Metastatic HER2-Positive Breast Cancer, New Treatments Emerge

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Two new treatment options are emerging for women with metastatic breast cancer, following positive results from clinical trials. The trials tested the drugs tucatinib and trastuzumab deruxtecan (Enhertu) in women who had been previously treated for metastatic breast cancer that overproduces the HER2 protein, known as HER2-positive breast cancer.

In one of the trials, called HER2CLIMB, women treated with tucatinib in addition to trastuzumab (Herceptin) and capecitabine lived longer both without their disease progressing and overall than women who received only trastuzumab and capecitabine (Xeloda). The treatment also benefited women in the trial whose cancer had spread to the brain, a particularly challenging group to treat.

Trastuzumab deruxtecan was tested in a smaller trial, called DESTINY-Breast01, and wasn't compared directly with another treatment. But many women in the study who received the drug saw their tumors shrink and lived for an extended period without their cancer getting worse.

Based on the DESTINY-Breast01 results, in fact, on December 20, the Food and Drug Administration (FDA) announced an accelerated approval for trastuzumab deruxtecan as a treatment for women with previously treated HER2-positive breast cancer. Under an accelerated approval, the drug's manufacturer, AstraZeneca, must conduct further studies of trastuzumab deruxtecan to confirm that it benefits patients.

Results from both clinical trials were presented in early December at the 2019 San Antonio Breast Cancer Symposium (SABCS) and published simultaneously in the New England Journal of Medicine.

Both drugs also can have significant side effects, the trials showed. In particular, trastuzumab deruxtecan caused lung-related side effects that led to several deaths. That finding led the study's leaders to stress that clinicians need to watch carefully for lung disease in women who receive the drug and take the appropriate measures to manage it.

FDA's approval of trastuzumab deruxtecan included a special warning for clinicians on the risk of the lung-related side effects, known as interstitial lung disease (ILD).

In both trials, women whose cancers had spread to the brain were eligible to participate. That's

important, explained Jesus Anampa, MD, who specializes in the treatment of breast cancer at the Montefiore Medical Center in New York. Breast cancer clinical trials often exclude women whose cancer has spread to the brain, but more than 25% of women with metastatic HER2-positive breast cancer will develop brain metastases, Anampa said.

In particular, the findings with tucatinib in women with brain metastases "are really impressive," he said. "The results are very exciting."

Different Drugs, Same Target

Breast cancers that are HER2-positive tend to be aggressive, with the excess HER2 protein on tumor cells fueling the cancer's growth. In the late 1990s, trastuzumab was among the first targeted cancer therapies to be approved by FDA, after trials showed it could improve survival in women with metastatic HER2-positive breast cancer.

Over time, other HER2-targeted therapies emerged, some with alternative mechanisms for disrupting HER2 activity in cancer cells. Drugs like trastuzumab and pertuzumab (Perjeta) are monoclonal antibodies that bind to the HER2 protein above the cancer cell's surface, preventing it from acting or enlisting the immune system to help destroy cells that produce it.

Tucatinib, on the other hand, is a member of a class of drugs known as tyrosine kinase inhibitors (TKIs). These drugs work by binding to the part of the HER2 protein that is inside the cell and preventing it from sending signals that promote cell growth. Other HER2-targeted TKIs include neratinib (Nerlynx) and lapatinib (Tykerb).

Some TKIs have multiple targets. But, compared with other HER2-targeted drugs, tucatinib appears to be relatively selective for HER2—that is, it's less likely to bind to related proteins, explained Stanley Lipkowitz, MD, PhD, chief of the Women's Malignancies Branch in NCI's Center for Cancer Research. That selectivity limits the risk of side effects seen with other HER2-targeted TKIs that inhibit other targets, Lipkowitz said.

Trastuzumab deruxtecan, meanwhile, is one of a class of drugs called antibody–drug conjugates (ADCs), which consist of a monoclonal antibody chemically linked to a cell-killing drug. Another ADC, trastuzumab emtansine (Kadcyla), or T-DM1, is already a standard treatment for metastatic HER2-positive breast cancer.

With ADCs, the antibody component serves as a homing device, guiding the linked drug to cancer cells. Once there, the ADC is shuttled inside the cell and the attached payload—in this case, the chemotherapy drug deruxtecan—is released, explained Ian Krop, MD, of Dana-Farber Cancer Institute, who led the DESTINY-Breast01 trial.

Deruxtecan is a type of chemotherapy drug called a topoisomerase I inhibitor, Krop said during an SABCS press briefing, but it is far more potent than other topoisomerase I inhibitors. And because deruxtecan is "membrane permeable," he said, it can then leave the target cancer cell and kill nearby cancer cells, "regardless of their HER2 expression."

Women in both the HER2CLIMB and DESTINY-Breast01 trials already had to have gone through at least two prior lines of treatment and all had received other HER2-targeted drugs, including trastuzumab, pertuzumab, and T-DM1, as part of those earlier treatments.

As such, both tucatinib and trastuzumab deruxtecan could meet an important need, Lipkowitz said, because there is no proven third-line treatment for metastatic HER2-positive breast cancer.

Tucatinib Improves Progression-Free Survival

Tucatinib was tested in the larger of the two trials. More than 600 participants were randomly assigned to receive either a commonly used third-line treatment regimen, the chemotherapy drug capecitabine and trastuzumab, along with a placebo, or treatment with the capecitabine–trastuzumab duo and tucatinib.

Women in the tucatinib group lived a little more than 2 months longer without their cancer getting worse (median of 7.8 months versus 5.6 months), an outcome known as progression-free survival, than women in the capecitabine–trastuzumab alone group.

In addition, nearly twice as many women in the tucatinib group saw their tumors shrink following treatment: 41% versus 23%. At 2 years after beginning treatment, approximately 45% of women in the tucatinib group were still alive, compared with approximately 27% in the other treatment group.

In women whose cancer had spread to the brain, which accounted for about 45% of trial participants, approximately 25% were still alive without their disease progressing 1 year after beginning treatment, compared with 0% in the other treatment group.

The trial's overall findings "are unprecedented for late-line therapy in advanced breast cancer," said its lead investigator, Rashmi Murthy, MD, of the University of Texas MD Anderson Cancer Center, in a press release.

Zeina Nahleh, MD, director of the Cleveland Clinic Florida's Maroone Cancer Center, agreed. Increasing survival in patients who have already received so many prior treatments "is a big achievement," Nahleh said.

Several side effects were more common in women in the tucatinib group, including diarrhea, vomiting, and fatigue. Severe diarrhea was also more frequent in women treated with tucatinib. Even so, less than 6% of patients in the tucatinib group stopped treatment because of side effects.

On December 23, Seattle Genetics, which manufactures tucatinib and funded the HER2CLIMB trial, announced that it had submitted its application to FDA for approval of the drug.

High Tumor Responses with Trastuzumab Deruxtecan

The DESTINY-Breast01 trial was not a randomized study, so all patients in the trial received

trastuzumab deruxtecan.

Nearly all of the more than 180 women in the trial had at least some reduction in the size of their tumors, with 61% experiencing substantial reductions, Krop reported. Several patients had no evidence of cancer following treatment, known as a complete response. The median progression-free survival was more than 16 months.

Krop called the results "compelling," noting that the tumor response rate is "roughly double or triple what we typically see in other studies of this third- or later-line [patient] population."

Most of the treatment-related side effects seen in the trial were mild, Krop said. Even so, 15% of the participants stopped taking the drug because of side effects. Nearly all of these women were those who experienced ILD. Four of the women who developed ILD died as a result.

"Why we have this particular risk is unclear," he said. "And clearly we need to do more … research to identify those patients who are at risk of getting the most severe cases of ILD and [learn] how to mitigate the risk."

For future studies of the drug, Krop said, clinicians will be advised to carefully monitor patients for any evidence or symptoms of ILD and, if they suspect it has developed, to immediately stop the drug and treat the patient with steroids.

Oncologists have become more comfortable dealing with lung-related side effects, Anampa said, particularly with the emergence of immunotherapies, several of which can also cause lung inflammation.

"We definitely have to be cautious," he continued. "But I don't think [ILD] is a major barrier to moving this drug forward."

FDA's approval of trastuzumab deruxtecan came approximately 2 months after AstraZeneca had filed its approval application. The agency had granted the application a "priority review," which is used to expedite the assessment of drugs it believes have the potential to be a significant improvement for the treatment of life-threatening conditions.

Looking Ahead

It will take time to see how these drugs will affect patients, Nahleh acknowledged.

"But it's a great opportunity to offer patients some options they currently don't have," she said.

Based on the HER2CLIMB results, Murthy believes that tucatinib, in combination with trastuzumab and capecitabine, "should be the new standard of care" for women with HER2-positive metastatic breast cancer who have gone through multiple lines of treatment.

Nahleh agreed, noting that, once approved, tucatinib would likely be the drug she would turn to in

this group of patients.

As for trastuzumab deruxtecan, Lipkowitz called it “a very exciting and promising agent.” Since both drugs (tucatinib and trastuzumab-deruxtecan) were given to similar patient groups, he said, it remains to be determined which patients are the best candidates for each drug.

The results of several ongoing phase 3 clinical trials of this drug will help oncologists better understand how trastuzumab deruxtecan should be used in clinical practice, he continued.

Of particular interest, he continued, is an ongoing study testing the drug in patients who have “HER2-low” cancer—that is, their tumors don’t express enough HER2 for them to be considered suitable candidates for HER2-targeted therapy using standard criteria.

Early results from this study showed that approximately 45% of women in the trial had a tumor response to the drug.

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