Drug Slows Progression in Refractory HER2+ Breast Cancer

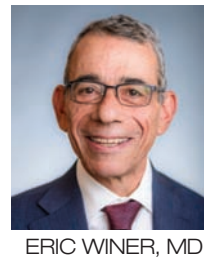
BY PETER M. GOODWIN

A new oral anti-human epidermal growth factor receptor 2 (HER2) drug, tucatinib, has slowed the progression of refractory metastatic HER2-positive breast cancer in patients who had been heavily pre-treated with chemotherapy and standard anti-HER2 agents. Results from the HER2CLIMB study were reported in the *New England Journal of Medicine* by an international team (2020;382:597-609).

"The biggest takeaway is that tucatinib in combination with trastuzumab and capecitabine reduced the risk of death by a third. It reduced the risk of progression or death by half. It nearly doubled the confirmed objective response rate," said lead author Rashmi Murthy, MD, MBE, Assistant Professor at the University of Texas MD Anderson Cancer Center.

RASHMI MURTHY, MD, MBE

She told *Oncology Times* that the benefits seen had been consistent across all of the pre-specified subgroups. "One of the most important features is that it is a very well-tolerated regimen. Most of the adverse events are low-grade [and] tend to be reversible, and there was a low rate of discontinuations—suggesting very good tolerability in heavily pre-treated patients."



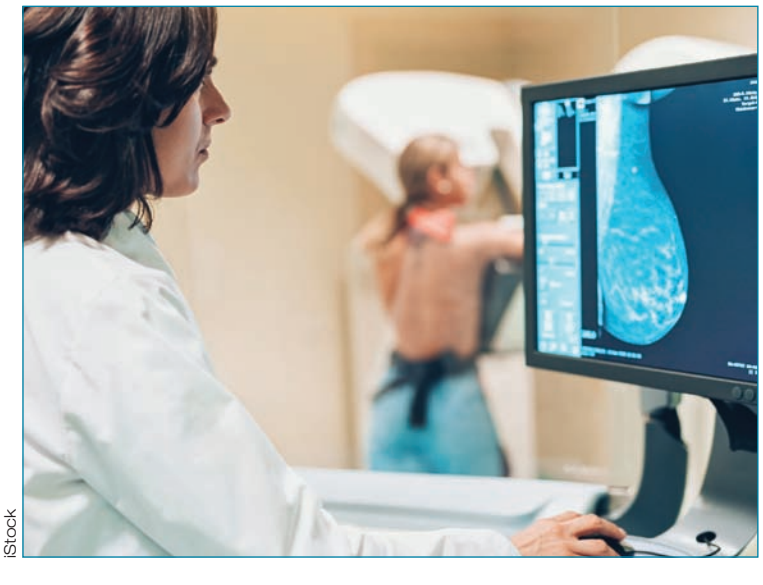
ERIC WINER, MD

Senior author Eric Winer, MD, Director of Breast Oncology at the Dana-Farber Cancer Institute, said that because tucatinib was a tyrosine kinase inhibitor specific for HER2, it had offered clinical benefits with fewer side effects than other HER2 agents.

"Unlike drugs like lapatinib and neratinib—which also inhibit either HER1 or HER4—tucatinib is a pure HER2 inhibitor. And as a result, it doesn't have diarrhea that comes with the inhibition of HER1," he said.

The other critical aspect of tucatinib that had been relevant for this study, Winer told *Oncology Times*, was that it had a very high degree of penetration into the brain. "So whereas most drugs are found in far lower concentrations in the brain than in the systemic circulation, tucatinib has a favorable profile in terms of brain penetration."

The 612-patient investigation had been a straightforward randomized study that compared a combination of tucatinib, capecitabine, and trastuzumab with a control arm of trastuzumab, capecitabine, plus a placebo, said Winer. He regarded HER2CLIMB as effectively double-blinded.



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"[In] general, the side effects of tucatinib were not significant enough that most patients or physicians could you tell whether the patient was on the standard arm or the tucatinib-containing arm," he explained.

The primary endpoint had been progression-free survival, and the study also assessed overall survival. Additionally, they also looked at both of these parameters in the sub-population of patients who had brain metastases.

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> *—Rashmi Murthy, MD, MBE, Assistant Professor at MD Anderson Cancer Center*

"What we found was that there was an improvement in progression-free survival. There was a statistically significant improvement in overall survival. And among the women who had brain metastases—either brain metastases that were relatively quiescent at the time of study entry, or brain metastases that were progressing—there was also an improvement in progression-free survival and an improvement in overall survival," Winer noted.

He said this had been the first agent demonstrating a survival advantage in patients with brain metastasis. "It is one of a limited number of agents that have shown an improvement in survival in metastatic breast cancer in general and specifically in HER2-positive breast cancer," Winer stated. "What it means is that we now have one more agent to use for the treatment of patients with metastatic HER2-positive breast cancer—and in particular, an agent that seems to be particularly effective in patients who have brain metastases."

HER2CLIMB assigned patients previously treated with trastuzumab, pertuzumab, and trastuzumab emtansine (TDM-1)—whether or not they had brain metastases—to be treated with either tucatinib or placebo, in combination with trastuzumab and capecitabine. The first 480 patients were assessed for the primary endpoint of progression-free survival and secondary endpoints were assessed in the total study population. These included overall survival, progression-free survival among patients with brain metastases, confirmed objective response rate, and safety.

A total of 33.1 percent of the patients were free of progression at 1 year in the tucatinib-combination group and 12.3 percent in the placebo-combination arm of the study. This gave a hazard ratio for disease progression or death of 0.54 (with a P-value less than 0.001).

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The median duration of progression-free survival was 7.8 months for patients treated with tucatinib and 5.6 months among those receiving placebo.

At 2 years, the overall survival rate was 44.9 percent among patients treated with the tucatinib combination and 26.6 percent in those receiving placebo. Median overall survival rates were 21.9 months for the tucatinib regimen and 17.4 months for the placebo combination.

Among patients with brain metastases, 24.9 percent experienced progression-free survival at 1 year in the experimental arm of the study and zero percent in the placebo combination group. The median progression-free survival was 7.6 months in the tucatinib arm and 5.4 months in the control arm.

Patients in the tucatinib group commonly had diarrhea, palmar–plantar erythrodysesthesia syndrome, nausea, fatigue, and vomiting. Diarrhea and elevated aminotransferase levels of grade 3 or higher were more common in the tucatinib combination group than in the placebo-combination group.

"We found that with the addition of tucatinib the risk of progression or death was reduced by 46 percent in the primary endpoint population, and median progression-free survival was improved from 5.6 months to 7.8 months with the addition of tucatinib," Murthy noted. "The second important finding was the risk of death was reduced by a third in the total population favoring patient who received tucatinib."

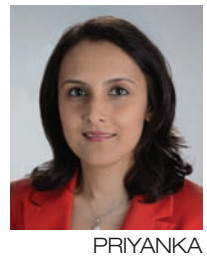
She regarded one of the most remarkable findings as the discovery that among patients with brain metastases the risk of progression or death had been reduced by half. "And when you look at the curve at the 1-year mark 25 percent of the patients who received tucatinib were still alive and without disease progression at 1 year, whereas all the patients on the control arm had experienced an event," she said.

Although Murthy regarded 25 percent as "still not good enough," she noted that it had been much better than having no patients at all without an event at the 1-year mark.

Murthy said the regimen had been very well-tolerated and that one of the important findings had been about toxicity. "Most toxicities were low-grade. Grade 1 or 2 diarrhea, hand-foot syndrome, nausea, fatigue, and vomiting were the most common things seen," she said. And a low rate of treatment discontinuation due to adverse events was reported. "Only 6 percent in the tucatinib arm and 3 percent in the control arm."

"In patients who were heavily pretreated—and exposed to all of our contemporary anti-HER2 targeted therapies, such as trastuzumab, pertuzumab, and TDM-1—we saw not only a progression-free survival benefit, but also a significant overall survival benefit. And that's something that we have not seen to date, and particularly not in the patient population that included those with active and progressing brain metastases," said Murthy.

Commenting in an editorial, Priyanka Sharma, MD, from the Department of Medicine's Division of Medical Oncology at the University of Kansas Medical Center, told *Oncology Times* she thought tucatinib, once approved, would become an important part of the treatment algorithm for patients with metastatic HER2-positive breast cancer.



PRIYANKA SHARMA, MD

"And the patients and providers will have yet another very active agent to treat the disease. Because of the biology, we have been successful in finding drugs that target so well. And how we choose this drug over others may be based on presence or absence of disease in the brain, the toxicity profile, [and] patient preference. But certainly to have a drug that not only has the overall efficacy but is showing efficacy indications [with] brain metastasis is remarkable—because that's an area of unmet need." OT

Peter M. Goodwin is a contributing writer.

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Learning Objectives for This Month's Activity:

After participating in this activity, readers should be better able to: 1. Identify the indication for and potential toxicities from tucatinib. 2. Evaluate results from the HER2CLIMB trial related to progression-free survival and overall survival with the use of tucatinib.

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