Drug Brings Marked Responses in Refractory HER2-Positive Breast Cancer

BY PETER M. GOODWIN

A new immunoconjugate drug has brought high overall response rates (ORR) and prolonged progression-free survival (PFS) in patients who had a median of six prior treatments for their HER2-positive breast cancer. The findings are from the DESTINY-Breast01 study published in the New England Journal of Medicine (2020; 382:610–621).

“This is an exciting and extremely active therapy for patients who already had two lines in the metastatic setting. When given with good vigilance and monitoring, this is a drug that provides meaningful anti-cancer benefits to our patients,” said lead author Shanu Modi, MD, Breast Medical Oncologist at Memorial Sloan Kettering Cancer Center in New York City.

“We have a number of wonderful therapies for people who have advanced stage HER2-positive breast cancer,” she told Oncology Times. “But once patients have gone through about two lines of some of our most potent drugs, there is still a group of patients that needs active agents. And the currently available therapies have really modest effects.”

New Immunoconjugate

Trastuzumab deruxtecan—also called DS-8201, now shortened to TDXD—was an antibody-drug conjugate targeting HER2 combining antigen specificity and targeted cytotoxicity, Modi said. “And we [already] have the experience of using [the HER2-targeted immunoconjugate trastuzumab emtansine] TDM1. TDXD is a little bit different. They both use trastuzumab as the antibody backbone. But that’s where the similarity ends. TDXD uses a very different chemotherapy payload: A topoisomerase 1 inhibitor.”

As this cytotoxic agent was not being used very often in breast cancer, patients didn’t usually get exposed to it, she explained. So, tumors were less likely already to have resistance mechanisms.

In a phase I dose-finding study, a majority of the patients with advanced HER2-positive breast cancer had responded to TDXD (median response duration, 20.7 months) and the investigators wanted to confirm whether the drug could benefit patients who had already been treated with TDM1.

The newly published results (that have already led to FDA approval) were from an open-label, single-group, phase II study of treatment with TDXD in women with HER2-positive metastatic breast cancer who had received previous treatment with TDM1.

The first part of the study evaluated three different doses to provide a “recommended dose,” which was then used in part two of the study to look at a primary endpoint of ORR and secondary endpoints of disease control rate, clinical benefit rate, duration of response, PFS, and safety.

Study Details

A total of 184 patients received the recommended 5.4 mg per kilogram of body weight dose of the immunoconjugate. And 112 patients (60.9%) responded to the drug for a median of 14.8 months with a median PFS of 16.4 months.

“The chemo linked to this antibody is very potent—10 times more potent than other topo I inhibitors used in cancer therapy. [And] there are twice as many molecules of the chemo per antibody as in TDM1. So, we can deliver a lot of this highly potent, really effective chemotherapy to the HER2-positive cells,” Modi said.

And she noted that another property of the drug was an advantage.

“This chemo is actually membrane permeable. So, it can pass through the cell membrane of one cell and then enter and kill surrounding, or neighboring cells, some of which may not even have the HER2 target—which is really unique. That’s what we call the bystander effect,” she said.

Modi explained that the drug had been active in early studies among heavily pre-treated patients and even in patients who had “HER2-low” breast cancer for which current HER2-targeted therapies were ineffective because of the relatively low expression of HER2.

“Incredible” Response Rate

Modi described the radiologically confirmed response rate of 61 percent as “pretty incredible.”

“Given all the prior therapy (a median six lines of treatment for metastatic disease), to see a response rate of 61 percent was pretty dramatic,” she stated.

Modi also emphasized the importance of response duration: “Almost as important as the response rate is how long the treatment benefits people. We saw a median duration of response of about 15 months. So, the average patient was staying on this drug for more than 1 year. Which is again, to me, just not seen in this line or this setting,” she said.

Putting the median PFS of just over 16 months in context, Modi noted: “[With] current available therapies for this third-line setting, we would expect to see a progression-free survival of 3-6 months. So, this was, again, really unexpected—really exciting—compelling data.”

Toxicity Noted

The investigators reported decreased neutrophil count (in 20.7% of patients) as the most common adverse event of grade 3 or higher.

The investigators reported decreased neutrophil count (in 20.7% of patients) as the most common adverse event of grade 3 or higher. Additionally, 8.7 percent of patients had anemia. Nausea affected 7.6 percent of patients had anemia. Nausea affected 7.6 percent of patients.

Modi said most toxicities were manageable. “We were able to get the nausea under control for the vast the majority of patients [and] we are very used to managing bone marrow suppression.” She said they found the lung toxicity could happen late: “Median onset is about 4 or 5 months. It is really critical for physicians and patients to be aware and report any new respiratory symptoms or worsening of respiratory symptoms.”

Continued on page 17

When given with good vigilance and monitoring, this is a drug that provides meaningful anti-cancer benefits to our patients.”

—Shanu Modi, MD, Breast Medical Oncologist at Memorial Sloan Kettering Cancer Center

10 Oncology Times March 20, 2020
Inflammation Caused By Radiation Drives Triple-Negative Breast Cancer

While radiation is successfully used to treat breast cancer by killing cancer cells, inflammation caused as a side effect of radiation can have a contrary effect by promoting the survival of triple-negative breast cancer cells, according to research published by Jennifer Sims-Mourtada, PhD, Director of Translational Breast Cancer Research at ChristianaCare’s Helen F. Graham Cancer Center & Research Institute (Int J Radiat Biol 2020:1-14). Accounting for 15-20 percent of all breast cancers, triple-negative breast cancer is faster growing than other types of breast cancers.

Sims-Mourtada’s latest study brings scientists closer to understanding the mechanisms behind this aggressive and hard-to-treat cancer. It shows that inflammation caused by radiation can trigger stem-cell-like characteristics in non-stem breast cancer cells.

“This is the good and the bad of radiation,” Sims-Mourtada stated. “We know radiation induced inflammation can help the immune system to kill tumor cells—that’s good—but also it can protect cancer stem cells in some cases, and that’s bad.”

“What’s exciting about these findings is we’re learning more and more that the environment the tumor is in—its microenvironment—is very important. Historically, research has focused on the genetic defects in the tumor cells. We’re now also looking at the larger microenvironment and its contribution to cancer.”

The term triple-negative breast cancer refers to the fact that the cancer cells don’t have estrogen or progesterone receptors and also don’t make too much of the protein called HER2. The cells test “negative” on all three tests. These cancers tend to be more common in women under age 40, who are African-American or Latina, or who have a BRCA1 mutation.

“My work focuses on cancer stem cells and their origination,” Sims-Mourtada said. “They exist in many cancers, but they’re particularly elusive in triple-negative breast cancer. Their abnormal growth capacity and survival mechanisms make them resistant to radiation and chemotherapy and help drive tumor growth.”

She and her team applied radiation to triple-negative breast cancer stem cells and to non-stem cells. In both cases, they found radiation induced an inflammatory response that activated the IL-6/Stat3 pathway, which plays a significant role in the growth and survival of cancer stem cells in triple-negative breast cancers. They also found that inhibiting STAT3 blocks the creation of cancer stem cells. Still unclear is the role IL-6/STAT3 plays in transforming a non-stem-cell to a stem-cell.

“At ChristianaCare, we are advancing cancer research to help people in our community today, while we also advance the fight against cancer nationwide,” said Nicholas J. Petrelli, MD, Bank of America Endowed Medical Director of the Helen F. Graham Cancer Center & Research Institute. “Dr. Sims-Mourtada’s research is a dramatic step toward better treatments for triple-negative breast cancer.”

To advance her research on inflammation, last year Sims-Mourtada received a grant from the Lisa Dean Moseley Foundation. The 3-year grant will enable her and her team at the Cawley Center for Translational Cancer Research to continue investigating the role of cells immediately around a tumor in spurring the growth of triple-negative breast cancer and a possible therapy for this particularly difficult cancer.

“Our next step is to understand the inflammatory response and how we might inhibit it to keep new cancer stem cells from developing,” Sims-Mourtada said.

Her research team previously identified an anti-inflammatory drug, currently used to treat rheumatoid arthritis, that has the potential to target and inhibit the growth of cancer stem cells and triple-negative breast cancer tumors. That research could set the stage for clinical investigation of the drug, alone or in combination with chemotherapy, to improve outcomes for patients with triple-negative breast cancer.

But she said the key was that TDXD was a really active drug. “I don’t think people should be afraid to use it. Overall, it is a another really exciting addition.” She was optimistic it would join the “toolbox” for patients with HER2-positive disease in the near future. “I want to have as many possible active options for my patients.”

Discussion

Commenting on the findings, Priyanka Sharma, MD, Professor of Medicine in the Division of Medical Oncology at the University of Kansas Medical Center in Kansas City, who wrote a commentary article on emerging HER2 therapies in the same edition of the New England Journal of Medicine, told Oncology Times this single-arm open-labelled trial had shown “very remarkable” results.

“It clearly demonstrated quite robust efficacy. And that led to approval of the drug in December. But there were some unique toxicities,” she said.

“The main toxicity that we are all talking about and are cautious about is interstitial lung disease, which was seen in about 15 percent of patients and actually lead to death in about 2 percent of patients. So, it was a serious toxicity. And it was not entirely clear why this toxicity was noted, which patients are most likely to suffer this toxicity, and how we should treat and manage it.

“So, we have to use judgment. And that requires close monitoring for signs and symptoms of interstitial lung disease (which is pulmonary symptoms, imaging abnormalities), and also paying close attention to baseline risk factors for interstitial lung disease before you recommend this drug. But clearly it is quite efficacious, and it will be used,” Sharma explained.

Peter M. Goodwin is a contributing writer.