Tucatinib Impresses in Breast Cancer

Seattle Genetics recently released data suggesting that tucatinib, when combined with trastuzumab (Herceptin; Genentech) and capecitabine, may effectively treat patients with locally advanced inoperable or metastatic HER2-positive breast cancer who have received prior therapies. In a phase II trial, the drug extended overall survival (OS) and progression-free survival (PFS) compared with trastuzumab and capecitabine alone and provided a PFS benefit in patients with brain metastases.

Patients with HER2-positive breast cancer usually receive trastuzumab and pertuzumab (Perjeta; Genentech) plus a taxane-based chemotherapy first, followed by T-DM1 (ado-trastuzumab emtansine, Kadcyla; Genentech) for progressive disease. Once the disease metastasizes, however, effective therapies are lacking, especially for the 30% to 50% of patients who also develop brain lesions.

Highly selective for HER2, tucatinib is a small-molecule tyrosine kinase inhibitor (TKI). In a phase Ib trial, tucatinib plus trastuzumab and capecitabine elicited responses in 14 of 23 patients, some of whom had brain metastases, and was generally well tolerated (Lancet Oncol 2018;19:880–8). Thus, the researchers decided to compare that three-drug combination with trastuzumab plus capecitabine alone in the randomized HER2CLIMB trial.

The trial included patients with locally advanced inoperable or metastatic HER2-positive breast cancer previously treated with trastuzumab, pertuzumab, and T-DM1. In the first 480 patients enrolled, the trial met its primary endpoint of PFS, with the tucatinib-containing regimen reducing the risk of disease progression or death by 46% compared with the trastuzumab–capecitabine control arm. Among 612 enrolled patients, two key secondary endpoints were also met—OS, as well as PFS in the 47% of patients who had brain metastases. Overall, tucatinib reduced the risk of death by 34% compared with trastuzumab plus capecitabine. Patients with brain metastases who received tucatinib had a 52% reduction in disease progression or death compared with those in the control arm.

The most common side effects in the tucatinib cohort were diarrhea, hand–foot syndrome, nausea, fatigue, and vomiting. In addition, adverse events of grade 3 or greater—namely diarrhea and elevated liver enzymes—were higher with tucatinib.

“This is some of the most exciting data I’ve seen in a long time,” says Sara Hurvitz, MD, of the University of California, Los Angeles, Jonsson Comprehensive Cancer Center, who is an investigator on the trial. Kevin Kalinsky, MD, of the Herbert Irving Comprehensive Cancer Center at Columbia University Irving Medical Center and New York-Presbyterian in New York, NY, who was not involved in the study, says he is particularly intrigued by the drug’s potential efficacy in patients with brain metastases.

“One of the big questions is going to be whether there may be activity for patients if you use it sooner in the disease course,” Kalinsky adds, and, if so, whether it can prevent brain metastases.

Hurvitz wants to know how tucatinib compares with the TKI neratinib (Nerlynx; Puma Biotechnology) as an adjuvant therapy, noting that the latter’s off-target effect on EGFR often causes severe side effects, namely diarrhea.

“Even as we began using words like ‘cold tumors’ to describe a lack of response to these drugs,” he remarked, “I thought another interpretation could simply be that this pathway isn’t used by many cancers” to escape immune surveillance. Indeed, PD-1–PD-L1 orchestrates such evasion in less than half of solid tumors, so Chen’s group set out to find additional operators of immune dysfunction in the tumor microenvironment (TME).

Using a functional screening assay to pinpoint modulators of T-cell activity, the researchers landed on Siglec-15. They found that it is minimally expressed in normal tissue, but widely upregulated on tumor cells and tumor-associated myeloid cells as well as M2 macrophages, leading to profound immunosuppression in the TME. How this happens is not fully understood, but “our data support a mechanism where Siglec-15—expressing cells can interact directly with T cells and shut them down,” Chen explained.

Notably, Siglec-15 expression is mutually exclusive with that of PD-L1: Where the latter is induced by IFNγ, Siglec-15 is downregulated—and vice
versa. “It’s why we think this is an independent, interesting target,” Chen added. A drug that alleviates Siglec-15–driven immunosuppression could be viable in patients who, with low or no PD-L1 expression, would not benefit from current checkpoint blockade.

Buoyed by preclinical results, Chen has been developing a Siglec-15 antibody, NC318, with Beltsville, MD–based biotech NextCure, for which he is the scientific founder. Preliminary findings from a phase I study of NC318 were highlighted during the Society for Immunotherapy of Cancer 2019 Annual Meeting in National Harbor, MD. Anthony Tolcher, MD, of NEXT Oncology in San Antonio, TX, reported that among 49 patients with a variety of tumor types, including non–small cell lung cancer (NSCLC), NC318 was safe and well tolerated. The main side effects were diarrhea and asymptomatic amylase and lipase elevations. Several cases of vitiligo—"considered a marker of immune activation," Tolcher said—were also observed.

Efficacy isn’t always seen in phase I trials, but two patients with NSCLC responded to NC318—one completely, the other partially. Both had received prior chemotherapy and PD-1 blockade, to which the best response was stable disease that then progressed. Noting that they had low levels of PD-L1, Tolcher agreed that NC318 could become a valuable therapy for this subset of patients, “where there’s a great unmet need” once disease progression occurs on standard treatment. Patients with several other tumor types experienced stable disease lasting at least 6 months.

Based on this early but encouraging efficacy, NC318 is undergoing phase II evaluation for NSCLC, as well as ovarian, head and neck, and triple-negative breast cancers. Chen hopes the data will hold up and pave the way for additional Siglec-15–targeted agents, potentially mirroring anti–PD-1 therapy’s success.

“Some recent prospective drugs have been more about boosting systemic immune responses to higher levels, which could result in unwanted issues,” he pointed out. Rather, “we believe normalizing defective immunity in the TME is something that can be done much more precisely, with minimal damage on the side.” –Alissa Poh

**Bempegaldesleukin Ups Melanoma Responses**

Preliminary findings of a phase I/II trial suggest that adding bempegaldesleukin (NKTR-214; Nektar Therapeutics) to the PD-1 checkpoint inhibitor nivolumab (Opdivo; Bristol-Myers Squibb) may lead to high overall and complete response rates, with relatively few side effects.

The data were presented by Adi Diab, MD, of The University of Texas MD Anderson Cancer Center in Houston, at the Society for Immunotherapy of Cancer (SITC) 2019 Annual Meeting in National Harbor, MD, in November. Bempegaldesleukin is a CD122–preferential IL2-pathway agonist. In preclinical studies, it increased tumor-infiltrating lymphocytes, T-cell clonality, and PD-1 expression—and expanded and activated CD8+ T cells and natural killer (NK) cells—leading researchers to hypothesize that it might improve responses to a PD-1 inhibitor. “It is likely a synergistic mechanism” in which bempegaldesleukin and nivolumab “activate the T cells in somewhat distinct but complementary ways,” says Douglas Johnson, MD, of Vanderbilt-Ingram Cancer Center in Nashville, TN, who was not involved in the trial.

The PIVOT-02 trial is testing bempegaldesleukin plus nivolumab in solid tumors. At SITC, researchers reported on 38 evaluable patients with newly diagnosed metastatic melanoma. After 18.6 months of follow-up, the combination had elicited responses in 20 patients, including 13 complete responses; median progression-free survival had not been reached. In total, 17.1% of patients experienced grade 3 or 4 adverse events, most commonly acute kidney injury or atrial fibrillation; 12.2% of patients discontinued one of the drugs due to side effects. “It is very promising activity in terms of high response rates, high complete response rates, early signs of durable responses, and excellent progression-free survival,” Johnson says. However, he adds that the results should be interpreted with caution given the study’s small size.

Moreover, he emphasizes that immune checkpoint inhibitor mono-therapy is associated with response rates of up to 40% to 45% in metastatic melanoma, so it is not clear how much bempegaldesleukin improves responses. “The gold standard is going to be randomized data comparing to nivolumab alone. That’s really the only way to truly determine whether the combination is adding something over nivolumab monotherapy,” he says.

Ryan Sullivan, MD, of Massachusetts General Hospital in Boston, who was also not involved in the trial, agrees. “I do think it’s encouraging; I just think it’s not game changing” without results from a larger, randomized trial, he says. He notes, however, that the combination is well tolerated compared with historical data on nivolumab monotherapy. “We’re seeing clearly that there doesn’t appear to be worse toxicity, and there may be some attenuation of the toxicity.”

A phase III trial is now comparing the combination with nivolumab in melanoma; other trials will test bempegaldesleukin in other combinations and tumor types. In particular, Johnson and Sullivan want to know whether bempegaldesleukin, either alone or in combination with nivolumab, is active in patients who develop resistance to immune checkpoint inhibitors. The agent may be effective in these patients, Sullivan explains, because it increases NK cells, which selectively attack cells that have lost MHC class I—a common state in resistant cells.

If the combination demonstrates effectiveness, clinicians would have another therapeutic option, one that may lead to more individualized treatment. Eventually, Johnson says, he hopes that researchers can identify biomarkers, and use them to match patients with treatment regimens. “We’re certainly not to that point yet,” he says, “but you can envision if you have another therapy like this, you can start to refine which patient populations need which thera-pies.” –Catherine Caruso

**Cancer Collaboration Aims to Boost Detection**

Cancer Research UK (CRUK) has launched a collaboration among three institutions in the UK and two in the United States to improve early cancer detection.

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