

# Highlights From the 2019 San Antonio Breast Cancer Symposium

Selected by Hope S. Rugo, MD

## Tucatinib Improves Survival in Metastatic HER2-Positive Breast Cancer

The addition of tucatinib to trastuzumab and capecitabine improved progression-free survival (PFS) and overall survival (OS) in heavily pretreated patients with metastatic human epidermal growth factor receptor 2 (HER2)-positive breast cancer, according to a primary analysis from the HER2CLIMB study. Tucatinib is an investigational inhibitor of the HER2 tyrosine kinase.

For the phase 2 study, which was also published in the December 11 issue of the *New England Journal of Medicine*, Dr Rashmi Murthy and colleagues enrolled patients with metastatic HER2-positive breast cancer who previously had been treated with trastuzumab, pertuzumab (Perjeta, Genentech), and trastuzumab emtansine (T-DM1; Kadcyla, Genentech). A total of 612 patients were randomly assigned to receive either tucatinib or placebo in combination with trastuzumab and capecitabine. Nearly half of the patients had past or current brain metastases.

Among the first 480 patients to undergo randomization, the 1-year PFS rate was 33.1% in the tucatinib group vs 12.3% in the placebo group (hazard ratio [HR] for disease progression or death, 0.54; 95% CI, 0.42-0.71;  $P < .001$ ). The median PFS was 7.8 vs 5.6 months, respectively.

Among the entire group of 612 patients, the 2-year OS rate was 44.9% in the tucatinib group vs 26.6% in the placebo group (HR for death, 0.66; 95% CI, 0.50-0.88;  $P = .005$ ), and the median OS was 21.9 vs 17.4 months, respectively. Among the patients with brain metastases, the 1-year PFS rate was 24.9% in the tucatinib group and 0% in the placebo group (HR, 0.48; 95% CI, 0.34-0.69;  $P < .001$ ), and the median PFS was 7.6 vs 5.4 months, respectively.

The most common adverse events (AEs) in the tucatinib group were diarrhea, palmar-plantar erythrodysesthesia syndrome, nausea, fatigue, and vomiting. Grade 3 or higher diarrhea and elevated aminotransferase levels were more common in the tucatinib group than in the placebo group.

Dr Murthy concluded that “tucatinib in combination

with trastuzumab and capecitabine has the potential to become a new standard of care in this patient population with and without brain metastases.”

## Margetuximab Improves PFS in Metastatic HER2-Positive Breast Cancer

Margetuximab improved PFS compared with trastuzumab in patients with pretreated, HER2-positive metastatic breast cancer, according to second interim results from the phase 3 SOPHIA study. Margetuximab is an experimental, Fc-engineered anti-HER2 monoclonal antibody.

For the study, Dr Hope Rugo and colleagues enrolled 536 women with metastatic HER2-positive breast cancer who had disease progression after 2 or more lines of anti-HER2 therapy that included pertuzumab. Patients were randomly assigned to chemotherapy plus either margetuximab or trastuzumab.

As reported at the 2019 annual meeting of the American Society of Clinical Oncology, when the data cutoff was October 2018, median PFS by central blinded analysis was significantly longer with margetuximab than with trastuzumab, at 5.8 vs 4.9 months, respectively (HR, 0.76; 95% CI, 0.59-0.98;  $P = .033$ ).

At the more recent data cutoff of September 2019, the investigator-assessed PFS was 5.7 months with margetuximab vs 4.4 months with trastuzumab (HR, 0.71; 95% CI, 0.58-0.86;  $P = .0006$ ). Also higher with margetuximab than with trastuzumab were the investigator-assessed objective response rate (25.2% vs 13.7%, respectively;  $P = .0006$ ) and the clinical benefit rate (48.1% vs 35.6%, respectively;  $P = .0025$ ). Although OS was not significantly longer with margetuximab than with trastuzumab in the overall group, it was significantly longer with margetuximab among the patients who were carriers of CD16A 158F, at 23.7 vs 19.4 months, respectively (HR, 0.79; 95% CI, 0.61-1.04;  $P = .087$ ).

Overall safety profiles were similar in the 2 groups, with grade 3 or higher AEs occurring in 53.8% of patients in the margetuximab group and 52.6% of those in the trastuzumab group. The discontinuation rates owing to AEs were 3.0% and 2.6%, respectively.

Dr Rugo concluded that “SOPHIA is the first trial

to show PFS superiority of a novel antibody compared to trastuzumab.” A final protocol-specified OS analysis is anticipated in late 2020.

### **Trastuzumab Deruxtecan Produces Good Response in Metastatic HER2-Positive Breast Cancer**

Trastuzumab deruxtecan, a novel antibody-drug conjugate, demonstrated a good objective response rate in patients with heavily pretreated HER2-positive metastatic breast cancer, according to results from the phase 2 DESTINY-Breast01 trial.

For the trial, Dr Ian Krop and colleagues evaluated 184 patients who received trastuzumab deruxtecan at a dosage of 5.4 mg/kg every 3 weeks for HER2-positive metastatic breast cancer. The patients were heavily pretreated, with a median of 6 prior lines of therapy in the advanced-disease setting. All patients had previously received treatment with T-DM1.

After a median follow-up of 11 months, the confirmed objective response rate by independent review was 60.9%, which comprised a complete response rate of 6.0% and a partial response rate of 54.9%. The 6-month clinical benefit rate was 76%, and the median duration of response was 14.8 months. The median time to response was 1.6 months, and the disease control rate was 97%. Fewer than 2% of the patients had disease progression at the first restaging. Median PFS was 16.4 months, and median OS was not reached.

The most common AEs were nausea, vomiting, and fatigue; nearly all of these were low-grade. Grade 3 or higher AEs occurred in 57% of patients. Trastuzumab deruxtecan was discontinued by 15% of the patients because of an AE; the most common reasons for discontinuation were pneumonitis and interstitial lung disease (ILD). ILD occurred in 25 patients and caused 4 deaths. An independent expert panel advised that patients should be monitored closely for symptoms of ILD in future trials, and that trastuzumab deruxtecan should be held and corticosteroids started as soon as ILD is suspected.

Dr Krop concluded that trastuzumab deruxtecan has the potential “to become a new standard of care for patients with pretreated advanced HER2-positive breast cancer.”

### **Six-Year APHINITY Results Strengthen Evidence for Pertuzumab in Early-Stage, HER2-Positive Breast Cancer**

The addition of pertuzumab to trastuzumab and chemotherapy improved the clinical outcomes in women with early-stage, HER2-positive breast cancer, according to second interim results from the phase 3 APHINITY trial.

The benefit of pertuzumab was particularly pronounced in those with high-risk disease, and occurred regardless of hormone receptor status.

The trial enrolled patients who had undergone surgery for early-stage, HER2-positive breast cancer. Dr Martine Piccart and coinvestigators randomly assigned 4805 patients to receive 1 year of treatment with either pertuzumab or placebo in addition to trastuzumab plus adjuvant chemotherapy.

After a median of 74.1 months (the previous analysis was at 45.4 months), 272 patients had died; this number represented 42.5% of the deaths needed for the definitive OS analysis. The difference in OS between the pertuzumab and placebo groups was not statistically significant, with a 6-year OS rate of 94.8% vs 93.9%, respectively (HR, 0.85; 95% CI, 0.67-1.07). An updated analysis of invasive disease-free survival (IDFS), however, strengthened the evidence of benefit with pertuzumab vs placebo in node-positive patients, with a 6-year IDFS rate of 87.9% vs 83.4%, respectively; HR, 0.72; 95% CI, 0.59-0.87). Pertuzumab benefit was seen in patients regardless of the hormone receptor status of their cancer, with an IDFS HR of 0.73 (95% CI, 0.59-0.92) in the hormone receptor-positive cohort and 0.83 (95% CI, 0.63-1.10) in the hormone receptor-negative cohort.

The analysis did not reveal any new cardiac safety issues with longer follow-up, and the incidence of primary cardiac events remained at less than 1% in both arms (0.8% with pertuzumab and 0.3% with placebo).

Dr Piccart said that the third interim analysis of OS will take place in 2022, and the definitive analysis will take place after 640 deaths have occurred.

### **T-DM1 Reduces Recurrences in Early-Stage HER2-Positive Breast Cancer**

Adjuvant T-DM1 monotherapy reduced recurrences compared with paclitaxel plus trastuzumab in stage I HER2-positive breast cancer, according to results from the phase 2 ATEMPT trial. These results represent the first report of patients receiving T-DM1 monotherapy for the adjuvant treatment of stage I HER2-positive disease, according to the study investigators.

Dr Sara Tolaney and her coinvestigators enrolled 512 patients with stage I HER2-positive breast cancer in the trial. Patients were randomly assigned in a 3:1 ratio to receive T-DM1 every 3 weeks for 17 cycles, or weekly paclitaxel/trastuzumab for 12 weeks followed by trastuzumab every 3 weeks for 13 cycles. The study was not powered to compare the efficacy of T-DM1 vs that of paclitaxel/trastuzumab but rather was powered to assess the 3-year disease-free survival rate for T-DM1 and to compare clinically relevant toxicities between the 2 arms.

After a median follow-up of 3.1 years, the 3-year

disease-free survival rate was 97.7% in the T-DM1 group. Although T-DM1 was not associated with significantly fewer clinically relevant toxicities than paclitaxel/trastuzumab, Dr Tolaney said that the regimens exhibited “differences in toxicity profiles.” Grade 2 or higher neurotoxicity was less frequent in the T-DM1 group than in the paclitaxel/trastuzumab group (11% vs 23%, respectively). On the other hand, patients in the T-DM1 group were more likely than those in the paclitaxel/trastuzumab group to discontinue therapy early because of toxicity (17% vs 6%, respectively). An examination of grade 2 or higher treatment-related AEs showed that patients in the T-DM1 group were more likely to have thrombocytopenia, elevated liver enzymes, and increases in bilirubin, whereas those in the paclitaxel/trastuzumab group were more likely to have neuropathy, neutropenia, and infusion-related reactions.

Dr Tolaney pointed out that the endpoint of clinically relevant toxicities does not capture all the toxicities that affect patient quality of life, such as alopecia. She added that evaluations of patient-reported outcomes, presented at the meeting by Partridge and colleagues and Ruddy and colleagues, favored T-DM1.

### Oral Paclitaxel Superior to Intravenous Paclitaxel in Metastatic Breast Cancer

Oral paclitaxel improved overall response in patients with metastatic breast cancer, as well as OS in some patients, when compared with intravenous (IV) paclitaxel, according to a phase 3 study. Patients in the oral paclitaxel group also received encequidar, an inhibitor of P-glycoprotein that increases the absorption of oral paclitaxel.

For the open-label study, Dr Gerardo Umancor and colleagues randomly assigned 402 patients in a 2:1 ratio to oral paclitaxel (205 mg/m<sup>2</sup> 3 days a week for 3 weeks) plus encequidar (OPE) or to IV paclitaxel (175 mg/m<sup>2</sup> every 3 weeks). Imaging was performed at baseline and at weeks 10, 16, and 19, and patients with a complete or partial response at week 19 received a confirmatory scan at week 22.

The prespecified modified intention-to-treat population, which included all patients with a baseline evaluable scan who received at least 7 doses of OPE and 1 dose of IV paclitaxel, contained 360 patients. The confirmed response rate among this group was significantly higher with OPE than with IV paclitaxel (40.4% vs 25.6%;  $P=.005$ ). The observed responses were relatively durable, with 74.7% of responses lasting longer than 100 days. Because multiple patients were still on treatment at the time of data cutoff, 33.7% of the responses lasted more than 200 days. Although data collection for median PFS was ongoing, a statistically nonsignificant trend favored OPE over paclitaxel (9.3 vs 8.3 months;  $P=.0773$ ). An

early analysis of median OS also favored OPE over paclitaxel (27.9 vs 16.9 months;  $P=.0353$ ).

The safety population, which included all patients enrolled in the study who received at least 1 dose of OPE or IV paclitaxel, included 399 patients. Regarding AEs of grade 2 or higher that occurred in at least 10% of the patients, OPE was associated with a lower incidence of neuropathy, alopecia, and pain but with higher rates of gastrointestinal toxicity, including diarrhea, nausea, vomiting, and abdominal pain. Regarding treatment-emergent AEs of interest, patients in the OPE group had less neuropathy and alopecia but more gastrointestinal toxicity.

Dr Umancor concluded that OPE is the first oral taxane regimen to demonstrate an improved and durable confirmed overall response compared with IV paclitaxel given every 3 weeks. “Oral paclitaxel and encequidar provides an important oral therapeutic option for patients with metastatic breast cancer, representing a meaningful improvement in the clinical profile of paclitaxel,” he said.

### Residual Cancer Burden Index Provides Important Prognostic Information in Breast Cancer

Measurement of the residual cancer burden (RCB) after neoadjuvant therapy provides important prognostic information in breast cancer, according to a pooled analysis of data by Dr Christina Yau and colleagues.

For the analysis, presented by Dr W. Fraser Symmans, researchers determined the RCB index of 5161 patients from 12 institutions and trials. RCB index values (obtained with the MD Anderson Residual Burden Calculator, available at [www.mdanderson.org/breastcancer\\_RCB](http://www.mdanderson.org/breastcancer_RCB)) ranged from 0 to III, with RCB-0 equivalent to a pathologic complete response, RCB-I equivalent to a minimal burden, RCB-II equivalent to a moderate burden, and RCB-III equivalent to an extensive burden of residual disease.

The researchers found that the event-free survival (EFS) event rate increased as the RCB index increased from RCB-I to RCB-III, and that EFS and distant relapse-free survival decreased as the RCB index increased from RCB-0 to RCB-III. The relationship between the RCB index and EFS persisted across breast cancer subtypes, including hormone receptor–negative, HER2–negative breast cancer; hormone receptor–negative, HER2–positive breast cancer; hormone receptor–positive, HER2–negative breast cancer; and hormone receptor–positive, HER2–positive breast cancer.

Dr Symmans concluded that the prognostic value of RCB applied to all 4 phenotypic subtypes of breast cancer studied, and that there is “a strong potential to calibrate an individual’s RCB index to residual prognostic risk.”