

Highlights in Breast Cancer From the 2022 American Society of Clinical Oncology Annual Meeting

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Trastuzumab Deruxtecan Improves Survival in HER2-Low Metastatic Breast Cancer

The antibody-drug conjugate (ADC) trastuzumab deruxtecan, also known as T-DXd (Enhertu, Daiichi-Sankyo/AstraZeneca), was shown to improve progression-free survival (PFS) and overall survival (OS) in comparison with standard chemotherapy in women who have human epidermal growth factor receptor 2 (HER2)-low metastatic breast cancer (mBC), according to a new study presented by Dr Shanu Modi and simultaneously published in the *New England Journal of Medicine*. The results, which were met with a standing ovation, are expected to change treatment for the approximately 50% of women who have mBC with low expression of HER2.

DESTINY-Breast04 was a multicenter, open-label, phase 3 study of 557 patients with HER2-low mBC who had received 1 or 2 prior lines of chemotherapy in the metastatic setting. HER2-low mBC was defined as a score of 1+ on immunohistochemistry (IHC) analysis or as an IHC score of 2+ and negative results on in situ hybridization. Patients were randomly assigned in a 2:1 ratio to T-DXd at 5.4 mg/kg or standard chemotherapy. The primary endpoint was PFS as determined by blinded independent central review (BICR) in patients with hormone receptor-positive (HR+) disease, who accounted for 88.7% of the total.

After a median follow-up of 18.4 months, the median PFS among women with HR+ disease was 10.1 months in the T-DXd group and 5.4 months in the standard chemotherapy group (hazard ratio [HR] for disease progression or death, 0.51; $P < .001$). Median OS among women with HR+ disease was 23.9 months in the T-DXd group and 17.5 months in the standard chemotherapy group (HR for death, 0.64; $P = .003$). Among all patients, the median PFS was 9.9 months in the T-DXd group and 5.1 months in the standard chemotherapy group (HR for disease progression or death, 0.50; $P < .001$), and the median OS was 23.4 months in the T-DXd group and 16.8 months in the standard chemotherapy group (HR for death, 0.64; $P = .001$).

Grade 3 or higher adverse events (AEs) occurred in

52.6% of the patients in the T-DXd group and 67.4% of those in the standard chemotherapy group. Treatment-related interstitial lung disease or pneumonitis occurred in 12.1% and was grade 5 in 0.8% of the patients in the T-DXd group.

“We have expanded the benefits of HER2-targeted therapy to a new population of breast cancer patients and have established T-DXd as the new standard of care for patients with HER2-low metastatic breast cancer,” Dr Modi concluded.

Modi S, Jacot W, Yamashita T, et al. Trastuzumab deruxtecan (T-DXd) versus treatment of physician's choice (TPC) in patients (pts) with HER2-low unresectable and/or metastatic breast cancer (mBC): results of DESTINY-Breast04, a randomized, phase 3 study [ASCO abstract LBA3]. *J Clin Oncol*. 2022;40(17)(suppl).

Sacituzumab Govitecan Improves PFS in Pretreated, HR+ Metastatic Breast Cancer

Sacituzumab govitecan (SG; Trodelvy, Gilead) improved PFS more than single-agent chemotherapy did in patients with heavily pretreated HR+, endocrine-resistant, unresectable locally advanced or metastatic BC, according to the results of the TROPiCS-02 study. The study did not identify any new safety signals with SG, which is an ADC directed against trophoblast cell surface antigen 2 (Trop-2).

Eligible patients for the phase 3 trial had unresectable locally advanced or metastatic HR+/HER2- BC and an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1, and had received 2 to 4 prior chemotherapy regimens for mBC. Patients were required to have received at least one prior taxane, a cyclin-dependent kinase (CDK) 4/6 inhibitor, and endocrine therapy. Dr Hope Rugo and colleagues enrolled 543 patients in a 1:1 ratio to receive SG or physician's choice of chemotherapy until disease progression or unacceptable toxicity. The primary endpoint was PFS by BICR.

After a median follow-up of 10.2 months, the median PFS was 5.5 months with SG vs 4.0 months with chemotherapy (HR, 0.66; 95% CI, 0.53-0.83; $P < .001$). Owing to rapid progression in a subset of patients in the first 2

months after starting study therapy, landmark analyses for PFS were also assessed. PFS was improved at 6, 9, and 12 months with SG, and the 12-month PFS rate was 21% in the SG group vs 7% in the chemotherapy group. At the first of 3 planned analyses for survival, the difference in OS—at 13.9 vs 12.3 months for SG vs chemotherapy, respectively—was not statistically significant (HR, 0.84; $P=.143$), but follow-up is ongoing. The objective response rate (ORR) and the clinical benefit rate (CBR) were both higher with SG than with chemotherapy, at 21% vs 14% and 34% vs 22%, respectively. Health-related quality of life was also better in the SG group than in the chemotherapy group, including a longer time until the development of fatigue.

Grade 3 or higher treatment-emergent AEs occurred in 74% of those in the SG group vs 60% of those in the chemotherapy group. AEs included neutropenia (51% vs 39%) and diarrhea (10% vs 1%), although there was no difference in the rates of febrile neutropenia. The rate of drug discontinuation owing to AEs was low in both arms, at 6% with SG vs 4% with placebo.

Dr Rugo concluded that SG “demonstrated significant, clinically meaningful benefit” in patients with heavily pretreated, endocrine-resistant, HR+/HER2– advanced breast cancer. She said that SG should be considered a potential treatment in these patients, for whom treatment options currently are limited.

Rugo HS, Bardia A, Marmé F, et al. Primary results from TROPiCS-02: a randomized phase 3 study of sacituzumab govitecan (SG) versus treatment of physician's choice (TPC) in patients (pts) with hormone receptor–positive/HER2–negative (HR+/HER2–) advanced breast cancer [ASCO abstract LBA1001]. *J Clin Oncol*. 2022;40(17)(suppl).

Ribociclib Improves PFS After Disease Progression in Metastatic Breast Cancer

The addition of ribociclib (Kisqali, Novartis) to treatment improved PFS in patients with HR+ mBC in whom endocrine therapy was being switched after disease progression during treatment with a CDK4/6 inhibitor, according to results of the MAINTAIN trial.

The multicenter, placebo-controlled, investigator-initiated phase 2 trial, which was presented by Dr Kevin Kalinsky, enrolled 120 patients with HR+/HER2– mBC whose cancer had progressed during treatment with CDK 4/6 inhibition and endocrine therapy. Patients were randomly assigned to ribociclib or placebo and in addition received endocrine therapy. Patients who had previously received fulvestrant received exemestane; those who had previously received exemestane received fulvestrant; and those who had received neither received whichever agent their doctor chose, although fulvestrant was encouraged. The primary endpoint was PFS. Palbociclib (Ibrance,

Pfizer) was the prior CDK4/6 inhibitor in 87% of patients.

After a median follow-up of 18.2 months, median PFS was 5.29 months in the ribociclib group vs 2.75 months in the placebo group (HR, 0.57; 95% CI, 0.39-0.95; $P=.006$). An exploratory analysis suggested that results in the subset of patients (83%) treated with fulvestrant were virtually identical to those in the full group; median PFS was 5.29 months in the ribociclib group vs 2.76 months in the placebo group (HR, 0.59; 95% CI, 0.39-0.94). The PFS rate was 41.2% with ribociclib vs 23.0% with placebo at 6 months and was 41.2% with ribociclib vs 23.0% with placebo at 12 months. Trends toward a higher ORR and CBR were noted for ribociclib vs placebo, but the differences were not statistically significant.

Neutropenia occurred in 72% of the ribociclib group vs 15% of the placebo group, and thrombocytopenia occurred in 25% of the ribociclib group vs 5% of the placebo group. Pneumonitis occurred in 3% of the ribociclib group vs 0% of the placebo group, and infection occurred in 10% of the ribociclib group vs 5% of the placebo group.

Dr Kalinsky concluded that ribociclib led to a statistically significant improvement in PFS in comparison with placebo in patients who had tumor progression following prior CDK4/6 inhibition, with ribociclib plus endocrine therapy demonstrating “a manageable and expected safety profile.”

Kalinsky K, Accordino MK, Chiuhan C, et al. A randomized, phase II trial of fulvestrant or exemestane with or without ribociclib after progression on anti-estrogen therapy plus cyclin-dependent kinase 4/6 inhibition (CDK 4/6i) in patients (pts) with unresectable or hormone receptor–positive (HR+), HER2–negative metastatic breast cancer (MBC): MAINTAIN trial [ASCO abstract LBA1004]. *J Clin Oncol*. 2022;40(17)(suppl).

Metastasis-Directed Treatment Does Not Improve Survival in Oligometastatic Breast Cancer

The addition of metastasis-directed treatment (MDT)—either stereotactic body radiotherapy, surgical resection, or both—did not improve PFS or OS in patients with oligometastatic breast cancer, according to a phase 2 randomized trial. Previous nonrandomized studies had suggested that this type of treatment might have value in these patients.

In the NRG-BR002 trial, Dr Steven J. Chmura and colleagues sought to determine whether the addition of MDT to standard-of-care (SOC) systemic therapy could improve PFS and OS in patients with oligometastatic breast cancer who had no more than 4 extracranial metastases and had been on SOC systemic therapy for no

more than 12 months without progression. Of the 129 randomized patients, 125 were considered eligible for the study and were assigned in a 1:1 ratio to SOC or SOC plus MDT as first-line therapy.

After a median follow-up of 35 months, the median PFS was 23 months in the SOC arm and 19.5 months in the MDT arm, a difference that was not statistically significant. The estimated PFS rate was 45.7% (95% CI, 38.9%-52.5%) in the SOC arm and 46.8% (95% CI, 39.2%-54.3%) in the MDT arm at 24 months, and was 32.8% (95% CI, 26.0%-39.5%) in the SOC arm vs 38.1% (95% CI, 29.7%-46.6%) in the MDT arm at 36 months. The median OS was not reached in either arm; OS rates at 36 months were 71.8% with SOC therapy and 68.9% with MDT. The addition of MDT did result in the development of fewer metastases inside the treated area but did not reduce the development of new metastases outside the treated area. Treatment-related AEs were mostly mild; grade 4 AEs developed in only 2% patients in the SOC group and no patients in the MDT group.

Dr Chmura concluded that although MDT is safe, with low rates of treatment-related AEs, the study did not show a signal for improved PFS with the addition of MDT. He added that this result was a “no-go signal” to proceed to phase 3 of the study.

Chmura SJ, Winter KA, Woodward WA, et al. NRG-BR002: A phase IIR/III trial of standard of care systemic therapy with or without stereotactic body radiotherapy (SBRT) and/or surgical resection (SR) for newly oligometastatic breast cancer (NCT02364557) [ASCO abstract 1007]. *J Clin Oncol*. 2022;40(16)(suppl).

Capivasertib Improves OS in Aromatase Inhibitor–Resistant, HR+ Advanced Breast Cancer

The addition of capivasertib to fulvestrant improved OS in women with aromatase inhibitor–resistant, HR+ advanced breast cancer, according to updated results from the phase 2 FAKTION trial, presented by Dr Robert Hugh Jones and simultaneously published in *Lancet Oncology*. In addition, biomarker analysis suggested that capivasertib—which is an experimental AKT kinase inhibitor—may primarily benefit patients who have tumors with PIK3CA/AKT1/PTEN pathway alterations.

In the FAKTION trial, 140 women with HR+/

HER2– metastatic or unresectable locally advanced BC whose disease had progressed on aromatase inhibition were randomly assigned in a 1:1 ratio to capivasertib plus fulvestrant or placebo plus fulvestrant. The primary endpoint was investigator-assessed PFS. In the primary analysis, which was reported in *Lancet Oncology* in 2020, the addition of capivasertib to fulvestrant more than doubled median PFS.

In the new data, which were collected after a median follow-up of 58.5 months in the capivasertib group and 62.3 months in the placebo group, fulvestrant still more than doubled the median PFS, from 4.8 to 10.3 months. Fulvestrant also improved the median OS, from 23.4 to 29.3 months (adjusted HR, 0.66; 95% CI, 0.45-0.97; $P=.035$). The updated analysis did not detect any new safety signals. The AEs that were more common in the capivasertib group than in the placebo group included diarrhea, rash, hyperglycemia, vomiting, infections, and oral mucositis. Only 1 grade 3 event (an infection) occurred with capivasertib.

Expanded testing with next-generation sequencing revealed PI3K/AKT/PTEN pathway alterations in the tumors of 54% of the participants, whereas original testing methods had detected these alterations in the tumors of 42% of the participants. Patients with PI3K/AKT/PTEN alterations were the most likely to derive benefit from capivasertib; in the patients with these alterations, median PFS was 12.8 months in the capivasertib group vs 4.6 months in the placebo group (HR, 0.44; 95% CI, 0.26-0.72; $P=.004$), and median OS was 39.8 months in the capivasertib group vs 20.0 in the placebo group (HR, 0.46; 95% CI, 0.27-0.79; $P=.005$). There was no statistically significant difference between capivasertib and placebo in PFS or OS in the patients without these alterations.

Dr Jones concluded that the data support the further development of capivasertib and added that the results of the phase 3 CAPItello-291 study, which is also looking at the addition of capivasertib to fulvestrant in HR+ breast cancer, “are awaited.”

Jones RH, Casbard AC, Carucci M, et al. Fulvestrant plus capivasertib versus fulvestrant plus placebo after relapse or progression on an aromatase inhibitor in metastatic, estrogen receptor–positive breast cancer (FAKTION): overall survival and updated progression-free survival data with enhanced biomarker analysis [ASCO abstract 1005]. *J Clin Oncol*. 2022;40(16)(suppl).