Highlights in Breast Cancer

Commentary by Hope S. Rugo, MD

Addition of Ribociclib to Endocrine Therapy Improves Outcomes in Early-Stage, HR+/HER2– Breast Cancer

The addition of ribociclib (Kisqali, Novartis) to endocrine therapy improves invasive disease–free survival (iDFS) in patients with early-stage, hormone receptor–positive (HR+)/human epidermal growth factor–negative (HER2–) breast cancer, according to the second interim results of the phase 3 NATALEE trial. Ribociclib has already been shown to improve survival in patients with metastatic HER+/HER2– breast cancer.

The trial, which was presented by Dr Dennis J. Slamon, enrolled 5101 pre- and postmenopausal patients with stage II or III HR+/HER2– breast cancer who were at risk for recurrence and had a European Cooperative Oncology Group performance status of 0 or 1. Patients were not required to have lymph node involvement. Patients were randomized in a 1:1 ratio to ribociclib (n=2549; 400 mg/day at 3 weeks on and 1 week off for 3 years) plus an aromatase inhibitor (AI; letrozole at 2.5 mg/day or anastrozole 1 mg/day for at ≥5 years) or an AI alone (n=2552). Men and premenopausal women also received goserelin. The primary endpoint was iDFS.

After a median follow-up of 34.0 months, 3810 (74.7%) of the patients remained on the study treatment (1984 in the ribociclib group and 1826 in the AI-alone group). After a median follow-up of 27.7 months, with a total of 426 events, iDFS was significantly longer with ribociclib than with an AI alone (hazard ratio [HR], 0.748; 95% CI, 0.618-0.906; *P*=.0014). The 3-year iDFS rate was 90.4% with ribociclib vs 87.1% with an AI alone, for an absolute difference of 3.3%. The benefit in iDFS was generally consistent across stratification factors and other subgroups, including a trend toward longer iDFS in patients with node-negative disease (HR, 0.63; 95% CI, 0.341-1.165). Patients in the ribociclib group also had better overall survival (OS), recurrence-free survival, and distant DFS compared with those in the AI-alone group. The safety profile of ribociclib at 400 mg was favorable, with no new safety signals. Adverse events (AEs) included all-grade neutropenia in 62.1% of ribociclib patients and 4.5% of AI-alone patients.

Dr Slamon concluded that these results "support ribociclib and nonsteroidal aromatase inhibitors as a new treatment of choice in a broad population" of patients with stage II or III, HR+/HER– breast cancer at risk for recurrence, including patients with node-negative disease.

Slamon DJ, Stroyakovskiy D, Yardley DA, et al. Ribociclib and endocrine therapy as adjuvant treatment in patients with HR+/HER2– early breast cancer: primary results from the phase III NATALEE trial [ASCO abstract LBA500]. *J Clin Oncol*. 2023;41(17)(suppl).

Commentary: NATALEE was the most anticipated breast cancer trial at this meeting, and it did not disappoint. The trial demonstrated an absolute improvement of 3.3% in iDFS with the addition of ribociclib to therapy in a relatively heterogeneous group of patients with metastatic HER+/HER2– breast cancer. This is certainly encouraging after just 2 years of follow-up. With longer follow-up, we hope to learn whether 3 years of therapy is superior to 2 years. Longer follow-up should also help determine whether ribociclib should be broadly applied to women who have higher-risk node-negative disease. These are areas in which the NATALEE study has the potential to make a tremendous impact. In addition, it was encouraging to see the decrease in hematologic toxicity with the 400-mg dose of ribociclib. Many of our patients are unable to tolerate abemaciclib (Verzenio, Lilly), even with dose reductions.

Study Supports Delay of CDK4/6 Inhibitors Until Second-Line Treatment in Advanced HR+/HER2– Breast Cancer

The use of cyclin-dependent kinase 4/6 (CDK4/6) inhibitors should be delayed until second-line treatment in patients with advanced HR+/HER2– breast cancer, according to the results of the phase 3 SONIA trial. First-line use of CDK4/6 inhibitors did not improve outcomes compared with second-line use and resulted in increased toxicity and costs.

For the trial, Dr Gabe S. Sonke and colleagues enrolled 1050 pre- and postmenopausal women from 74 Dutch hospitals who had not received prior therapy for advanced breast cancer. Participants were required to have a World Health Organization performance status of 0 to 2, and prior neoadjuvant or adjuvant therapy was allowed if the interval since an AI was at least 12 months. Patients were randomly assigned in a 1:1 ratio to receive first-line treatment with a CDK4/6 inhibitor plus an AI, followed on progression by fulvestrant (strategy A), or first-line treatment with an AI, followed on progression by fulvestrant plus a CDK4/6 inhibitor (strategy B). The primary endpoint was time from randomization to progression on second-line treatment or death (PFS2).

After a median follow-up of 37.3 months, the median

time on CDK4/6 inhibition was 24.6 months with strategy A and 8.1 months with strategy B, a difference of 16.5 months. The median PFS2 was not significantly better with strategy A than with strategy B, at 31.0 vs 26.8 months, respectively (HR, 0.87; 95% CI, 0.74-1.03; *P*=.10). The median OS also was not significantly better with strategy A than with strategy B, at 45.9 vs 53.7 months, respectively (HR, 0.98; 95% CI, 0.80-1.20; *P*=.83). Measures of quality of life did not detect a difference between the study arms, but the use of strategy A increased the cost of treatment by an average of $200,000 per patient. The side effects of CDK4/6 inhibition were consistent with those in previous studies, but there were 72% more grade 3 or 4 AEs with strategy A (2782) than with strategy B (1620).

Dr Sonke concluded that "SONIA challenges the need for using CDK4/6 inhibitors as first-line treatment. For many patients, particularly in the first-line setting where resistance mechanisms are less prevalent, endocrine therapy alone remains an excellent option."

Sonke GS, Van Ommen-Nijhof A, Wortelboer N, et al. Primary outcome analysis of the phase 3 SONIA trial (BOOG 2017-03) on selecting the optimal position of cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors for patients with hormone receptor-positive (HR+), HER2-negative (HER2-) advanced breast cancer (ABC) [ASCO abstract LBA1000]. *J Clin Oncol*. 2023;41(17)(suppl).

Commentary: The SONIA trial brought up a lot of questions. The trial failed to demonstrate any difference in long-term outcomes when CDK4/6 inhibition was given in the second-line metastatic setting, after progression, vs the first-line metastatic setting. It showed that patients with advanced HR+/HER2– breast cancer could receive a much shorter course of treatment with an expensive drug and achieve the same long-term outcome. What does this mean for our patients? One unanswered question is what treatment was offered to patients after PFS2. Now that we have new targeted therapies that can be combined with fulvestrant (such as elacestrant [Orserdu, Stemline], which has been approved for patients with mutated *ESR1*) and new oral selective estrogen receptor degraders are becoming available, the data from SONIA may be less pertinent to most of our patients.

Fixed-Dose vs Standard-Dose Capecitabine Maintains Survival, Decreases Toxicity in Metastatic Breast Cancer

Fixed-dose capecitabine provides progression-free survival (PFS) and OS rates that are comparable to those with standard-dose capecitabine in patients with metastatic breast cancer but with less toxicity, according to the results of the X-7/7 trial. Identifying effective therapy with less toxicity is important for patients with metastatic breast cancer, said presenter Dr Qamar J. Khan, because they remain on continuous treatment.

Patients with metastatic breast cancer were eligible for the study regardless of the number of prior lines of endocrine therapy or chemotherapy they had received, and HER2+ patients were eligible if they received concurrent trastuzumab. The primary endpoint was 3-month PFS. Patients were randomly assigned in a 1:1 ratio to receive either standard-dose capecitabine at 1250 mg/m^2 twice daily, 14 days on followed by 7 days off (n=73), or fixed-dose capecitabine at 1500 mg twice daily, 7 days on followed by 7 days off (n=80). Breast cancer was HR+/HER2– in 78% of patients, HER2+ in 11%, and triple-negative in 11%.

The researchers found that the 3-month PFS was 76% in both arms (HR, 1.01; 95% CI, 0.52-1.94; *P*=.99). In addition, PFS for fixed-dose vs standard-dose capecitabine was 39% vs 50% at 12 months (*P*=.23), 25% vs 23% at 24 months (*P*=.77), and 11% vs 0% at 36 months (*P*=.24), respectively. The restricted mean PFS at 36 months was 13.9 months in the fixed-dose arm vs 14.6 months in the standard-dose arm. The restricted mean OS at 47 months was 24.5 months in the fixed-dose arm vs 20.9 months in the standard-dose arm.

The landmark analysis of OS for fixed-dose vs standard-dose capecitabine was 94% vs 85% at 3 months (*P*=.16), 56% vs 63% at 12 months (*P*=.59), 30% vs 33% at 24 months (*P*=.85) 23% vs 23% at 36 months (*P*=1.0), and 17% vs 14% at 48 months (*P*=.82), respectively. Patients receiving fixed-dose capecitabine were less likely than those receiving standard-dose capecitabine to experience grade 2 to 4 toxicities (25.0% vs 49.3%; *P*=.0018), including diarrhea (2.5% vs 20.5%; *P*=.0008) and hand-foot syndrome (3.8% vs 15.1%; *P*=.0019). The discontinuation rate was significantly lower with fixed-dose capecitabine compared with standard-dose capecitabine, at 7.5% vs 28.7%, respectively (*P*<.001).

"Fixed-dose [capecitabine] may be an alternative dosing option to minimize toxicity while maintaining outcomes in metastatic breast cancer," Dr Khan concluded.

Khan QJ, Bohnenkamp C, Monson T, et al. Randomized trial of fixed dose capecitabine compared to standard dose capecitabine in metastatic breast cancer: the X-7/7 trial [ASCO abstract 1007]. *J Clin Oncol*. 2023;41(16)(suppl).

Commentary: Many investigators have suggested that giving a fixed dose of capecitabine may be as effective as the standard-dose capecitabine for treating patients with breast cancer. However, data from randomized trials to support this approach have been limited until this study came about. The X-77 trial showed that the 2 schedules had

similar PFS and OS results, and that fixed-dose capecitabine led to reduced toxicity. This was especially notable for high-grade diarrhea and hand-food syndrome, where there was a dramatic difference. The main caveats are that this was a small study, with only 73 patients in the standard arm and 80 patients in the experimental arm, and that the dose used in the control arm (1250 mg/m^2 twice daily) is not what we use in clinical practice in the United States (2000 mg/m^2 twice daily). Still, I think that the 1250-mg/m^2 dose is a reasonable option.

Response-Adapted Strategy Allows Many Patients With HER2+ Early Breast Cancer to Skip Chemotherapy

Chemotherapy can be omitted in approximately one-third of patients with HER2+ early breast cancer by first measuring their response to neoadjuvant trastuzumab plus pertuzumab (Perjeta, Genentech), according to the results of the PHERGain study. Dr Javier Cortés presented the most recent follow-up of this study, which demonstrated that conditional chemotherapy led to a favorable 3-year iDFS rate.

The conditional chemotherapy group consisted of 285 patients with centrally-confirmed, stage I to IIIA, HER2+ breast cancer who received neoadjuvant trastuzumab plus pertuzumab, either with or without endocrine therapy. If patients did not respond to treatment after 2 cycles, based on positron emission tomography (PET) results or pathologic complete response (pCR), they received chemotherapy. A total of 267 patients (93.7%) proceeded to surgery. The coprimary endpoints were pCR in responders by PET, and 3-year iDFS.

In the previous results, which were published in the *Lancet Oncology* in 2021, the pCR rate among PET responders at 5.7 months of follow-up was 37.9%. In the new results, the researchers found that the 3-year iDFS rate among the patients receiving conditional chemotherapy was 95.4% (95% CI, 92.8 to 98.0), which met the second primary endpoint (*P*<.001). After a median follow-up of 43.3 months (range, 2.4-63.0), a total of 12 iDFS events were reported, including 8 distant recurrences (3.0%), 3 locoregional ipsilateral recurrences (1.1%), and 1 nonrelated death (0.4%). Among the 86 patients with a pCR who did not receive chemotherapy as part of study treatment, only 1 patient had an invasive event, making the 3-year iDFS rate 98.8% (95% CI, 96.3 to 100.0). Patients in a control group of 71 patients who automatically received chemotherapy had a higher rate of grade 3 or higher treatment-related AEs than those in the conditional chemotherapy group, at 61.8% vs 32.9%, respectively (*P*<.001), and a higher rate of serious AEs, at 27.9% vs 13.8%, respectively (*P*=.01). No treatment-related deaths were reported.

Dr Cortés said that the results of conditional therapy were "in line with those reported with the combination of chemotherapy plus dual HER2 blockade."

Cortés J, Pérez-García JM, Ruiz-Borrego M, et al. 3-year invasive disease-free survival (iDFS) of the strategy-based, randomized phase II PHERGain trial evaluating chemotherapy (CT) de-escalation in human epidermal growth factor receptor 2-positive (HER2[+]) early breast cancer (EBC) [ASCO abstract LBA506]. *J Clin Oncol*. 2023;41(17)(suppl).

Commentary: The data from PHERGain are fascinating, and I expect them to affect the design of future studies. PHERGain showed that a percentage of patients with HER2+ early breast cancer can be effectively treated with trastuzumab and pertuzumab alone, without the need for chemotherapy, if they exhibit an early response based on pCR. This finding challenges us to identify which patients can be treated with antibody therapy alone and still have an excellent outcome. Although these patients are in the minority, it is crucial to identify them. According to a June 15 press release from Reveal Genomics, the pCR score on the HER2DX genetic test was significantly associated with pCR in the PHERGain trial.

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