Highlights in Breast Cancer From the 2018 American Society of Clinical Oncology Annual Meeting

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Commentary by Hope S. Rugo, MD

More Women With Early-Stage Hormone-Sensitive Breast Cancer Can Skip Chemotherapy

Chemotherapy does not benefit a large subset of women with breast cancer who are at intermediate risk for recurrence, according to a study presented by Dr Joseph A. Sparano of the Albert Einstein Cancer Center in New York, New York. The study, called TAILORx (Trial Assigning Individualized Options for Treatment), looked specifically at women with hormone receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative, node-negative breast cancer, who account for half of all patients with breast cancer in the United States.

A total of 10,273 women with this form of breast cancer were assigned to 1 of 3 groups depending on their 21-gene test (OncoType DX, Genomic Health) recurrence score. Those at low risk (score, 0-10) received endocrine therapy (1629 patients), those at intermediate risk (score, 11-25) were randomly assigned to endocrine therapy alone (3399 patients) or endocrine therapy plus chemotherapy (3312 patients), and those at high risk (score, 26-100) were assigned to endocrine therapy plus chemotherapy (1389 patients).

At 9 years, the rate of distant recurrence was 3% in the low-risk group, 5% in the intermediate-risk group, and 13% in the high-risk group. Among the patients in the intermediate-risk group, endocrine therapy alone was noninferior to endocrine therapy plus chemotherapy for all endpoints measured: invasive disease–free survival (83.3% vs 84.3%), distant relapse–free survival (94.5% vs 95.0%), relapse-free interval (92.2% vs 92.9%), and overall survival (OS; 93.9% vs 93.8%). Dr Sparano concluded that there was "no evidence for chemo benefit" among women with an intermediate risk score. The chemotherapy benefit for invasive disease–free survival varied with the combination of recurrence score and age (P=.004). Women 50 years of age or younger, however, derived some benefit from chemotherapy if their recurrence score was 21 to 25—at the higher end of the intermediate range.

The results were published July 12 in the *New England Journal of Medicine*.

Sparano JA, Gray RJ, Wood WC, et al. TAILORx: phase III trial of chemoendocrine therapy versus endocrine therapy alone in hormone receptor-positive, HER2-negative, node-negative breast cancer and an intermediate prognosis 21-gene recurrence score [ASCO abstract LBA1]. *J Clin Oncol*. 2018;36(15)(suppl).

Commentary: We now have 2 large prospective studies in which gene expression assays were used that can help determine whether patients with early-stage, hormone receptor–positive breast cancer are more or less likely to benefit from adjuvant chemotherapy. TAILORx provides important information regarding prognostic and treatment differentiation in a group of patients with node-negative, hormone receptor–positive disease. Overall, patients with a risk score of 25 or less had a very good prognosis with adjuvant endocrine therapy alone. Subset differences, especially in younger patients with scores from 21 to 25, are intriguing and consistent with what we expect to see in a heterogeneous disease that is affected by clinicopathologic variables. Of interest, the group with high scores had a worse outcome even though these patients received chemotherapy. The take-home messages are these: (1) we can use chemotherapy in fewer patients with node-negative, hormone receptor–positive breast cancer; (2) clinicopathologic factors still really matter and need to be considered along with the risk score; and (3) we need better treatments for node-negative, high-risk cancers.

Shorter Course of Trastuzumab Noninferior to Longer Course

Adjuvant treatment with trastuzumab (Herceptin, Genentech) for 6 months is noninferior to adjuvant treatment for 12 months in patients with HER2-positive early breast cancer, according to results of the phase 3 PERSEPHONE trial (Trastuzumab in Treating Women With HER2-Positive Early Breast Cancer). This finding is important because shortening the duration of therapy can reduce toxicities and cost.

For the trial, Dr Helena Earl of the University of Cambridge in Cambridge, the United Kingdom, and colleagues randomly assigned 4088 patients at 152 sites in the United Kingdom with HER2-positive early breast cancer to receive adjuvant trastuzumab for 6 or 12 months between 2007 and 2015.

At a median follow-up of 5.4 years, 335 deaths (8%) and 512 disease-free survival (DFS) events (13%) had occurred. The 4-year DFS rates were 89.4% with 6 months of treatment and 89.8% with 12 months of treatment, and the calculated hazard ratio (HR) of 1.07 (90% CI, 0.93-1.24; *P*=.01) for 6 months of treatment was within the noninferiority limit. The 4-year OS rate with 6 months of treatment also was noninferior compared with 12 months. Patients in the 6-month group were less likely than those in the 12-month group to halt treatment because of cardiotoxicity (4% vs 8%; *P*<.0001) and were less likely to experience a grade 3 or 4 adverse event during treatment (23% vs 18%; *P*=.004).

Certain patient subgroups did seem to benefit more from 12 months of treatment, specifically those who received trastuzumab concurrently with chemotherapy and those who received taxane-based therapy.

Dr Earl concluded that "6 months of adjuvant trastuzumab is noninferior to 12 months," and that shortening the duration of treatment "reduces cardiac and other toxicities." Future analyses of this trial will look at patient-reported quality of life and health care costs, as well as translational endpoints.

Earl HM, Hiller L, Vallier AL, et al. PERSEPHONE: 6 versus 12 months (m) of adjuvant trastuzumab in patients (pts) with HER2 positive (+) early breast cancer (EBC): randomised phase 3 non-inferiority trial with definitive 4-year (yr) disease-free survival (DFS) results [ASCO abstract 506]. *J Clin Oncol*. 2018;36(15)(suppl).

Commentary: PERSEPHONE is the third and largest of the prospective trials evaluating 6 vs 12 months of adjuvant trastuzumab for early-stage, HER2-positive breast cancer. An additional 2 trials evaluated 9 weeks vs 12 months. All of the trials were designed as noninferiority trials, meaning that the difference between the observed outcome in the control and experimental arms had to fall within a predefined margin. A positive trial result, of course, is therefore determined by how the margin was set. Patients enrolled in PERSEPHONE largely had lower-risk disease, received trastuzumab after adjuvant chemotherapy, and received a chemotherapy regimen that is infrequently used today (anthracyclines without taxanes). It is very encouraging to see excellent outcomes in patients enrolled in PERSEPHONE and a very narrow difference well within the predefined margin, demonstrating noninferiority for the shorter regimen. However, none of the other trials previously noted met their noninferiority endpoint. How do we interpret such variable results? My take is that PERSEPHONE demonstrates that low-risk disease (node negativity, smaller tumor size) is probably adequately treated with 6 months of adjuvant trastuzumab given concurrently with chemotherapy, and that this will reduce toxicity, particularly in our older patients.

Taselisib Modestly Improves PFS at the Cost of Toxicity in Advanced *PIK3CA*-Mutated Breast Cancer

Adding taselisib to treatment with fulvestrant (Faslodex, AstraZeneca) improves progression-free survival (PFS) in patients with estrogen receptor–positive, HER2-negative, *PIK3CA*-mutated locally advanced or metastatic breast cancer, according to a new study. Taselisib is a potent selective inhibitor of phosphoinositide 3-kinase (PI3K).

For the phase 3 SANDPIPER trial (A Study of Taselisib + Fulvestrant Versus Placebo + Fulvestrant in Participants With Advanced or Metastatic Breast Cancer Who Have Disease Recurrence or Progression During or After Aromatase Inhibitor Therapy), Dr José Baselga of Memorial Sloan Kettering Cancer Center in New York, New York, and colleagues identified 516 postmenopausal patients with this form of breast cancer who experienced disease recurrence or progression during or after aromatase inhibitor treatment. Patients were randomly assigned in a 2:1 ratio to receive fulvestrant alone or in combination with taselisib.

The researchers found that patients in the taselisib/fulvestrant group had a significantly longer investigator-assessed median PFS than did those in the fulvestrant-alone group: 7.4 vs 5.4 months (HR, 0.70; *P*=.0037). Patients in the combination group also had a better objective response rate (ORR), clinical benefit rate, duration of response, and PFS by blinded independent central review compared with those in the fulvestrant-alone group. OS data were immature.

The most common grade 3 or 4 adverse events in the taselisib/fulvestrant group were diarrhea (12%), hyperglycemia (10%), colitis (3%), and stomatitis (2%). Patients in the taselisib/fulvestrant group were more likely than those in the fulvestrant-alone group to discontinue treatment (17% vs 2%) or reduce their medication dose (37% vs 2%) because of adverse events.

Dr Baselga cautioned that despite the improvement in investigator-assessed PFS and other endpoints with taselisib/fulvestrant, "the challenging tolerability of this combination led to frequent discontinuations, and may

have limited the clinical benefit in this disease setting."

Baselga J, Dent SF, Cortés J, et al. Phase III study of taselisib (GDC-0032) + fulvestrant (FULV) v FULV in patients (pts) with estrogen receptor (ER)-positive, PIK3CA-mutant (MUT), locally advanced or metastatic breast cancer (MBC): primary analysis from SANDPIPER [ASCO abstract LBA1006]. *J Clin Oncol*. 2018;36(15)(suppl).

Commentary: Taselisib is the third small-molecule PI3K inhibitor to be tested in a prospective randomized trial in combination with fulvestrant. The pan-PI3K inhibitor buparlisib minimally improved PFS in 2 randomized phase 3 trials in combination with fulvestrant compared with fulvestrant alone, but a subset analysis suggested greater benefit in those patients whose tumors had *PIK3CA* mutations. However, because hepatic and central nervous system toxicity limited treatment, development was discontinued. Another pan-PI3K inhibitor, pictilisib, failed to improve PFS in a randomized phase 2 trial. Taselisib is a β-sparing inhibitor, and significant gastrointestinal toxicity (thought to be due to its inhibition of PI3K-δ and PI3K-γ) as well as hyperglycemia limited drug exposure in this trial, which focused on patients whose tumors had *PIK3CA* mutations. Although PFS was improved by a modest 2 months, toxicity outweighed benefits, leading to the discontinuation of taselisib development on the day the data were presented. We know that drugs of this class have efficacy—particularly in *PIK3CA*-mutated tumors—and that *PIK3CA* mutations occur in 40% or more of progressing hormone receptor–positive breast cancers, but finding the right drug and balancing efficacy against toxicity has proved to be frustratingly difficult. Results from SOLAR11, an additional trial with a more α-specific PI3K inhibitor, alpelisib, are slated to be presented this fall. We await results of this trial with excitement and a bit of trepidation.

Ribociclib Improves PFS in Advanced Breast Cancer

The addition of ribociclib (Kisqali, Novartis) to treatment with fulvestrant improves PFS in postmenopausal women with hormone receptor–positive, HER2-negative advanced breast cancer, according to the results of the phase 3 MONALEESA-3 trial (Study of Efficacy and Safety of LEE011 in Men and Postmenopausal Women With Advanced Breast Cancer). Ribociclib is an inhibitor of CDK4/6.

For this study, Dr Dennis J. Slamon of the UCLA Medical Center in Santa Monica, California, and colleagues looked at patients with this form of breast cancer who had previously received no or 1 line of endocrine therapy. A total of 726 patients were randomly assigned in a 2:1 ratio to treatment with ribociclib/fulvestrant or with fulvestrant alone.

After a median duration of follow-up from randomization of 20.4 months, median PFS was significantly longer in the ribociclib/fulvestrant arm than in the placebo/fulvestrant arm: 20.5 vs 12.8 months (HR, 0.593; 95% CI, 0.480-0.732; P=4.10×10^{-7}). Blinded independent review of the data supported these primary efficacy results. Patients experienced a PFS benefit whether they had previously received no endocrine therapy or 1 line of endocrine therapy.

Common adverse events in the ribociclib/fulvestrant and placebo/fulvestrant arms, respectively, included neutropenia (70% vs 2%), nausea (45% vs 28%), and fatigue (31% vs 33%). Grade 3 or 4 neutropenia, elevated alanine aminotransferase, and elevated aspartate aminotransferase were all more common with ribociclib/fulvestrant than with placebo/fulvestrant.

Dr Slamon concluded that ribociclib/fulvestrant "represents a new first- or second-line treatment option for postmenopausal women with hormone receptor–positive, HER2-negative advanced breast cancer."

The results of the study were published online June 3 in the *Journal of Clinical Oncology*.

Slamon DJ, Neven P, Chia SKL, et al. Ribociclib (RIB) + fulvestrant (FUL) in postmenopausal women with hormone receptor-positive (HR+), HER2-negative (HER2–) advanced breast cancer (ABC): results from MONALEESA-3 [ASCO abstract 1000]. *J Clin Oncol*. 2018;36(15)(suppl).

Commentary: MONALEESA-3 is the last of the randomized phase 3 trials testing CDK4/6 inhibitors in metastatic hormone receptor–positive breast cancer to be reported. Ribociclib is 1 of 3 FDA-approved CDK4/6 inhibitors, including palbociclib (Ibrance, Pfizer) and abemaciclib (Verzenio, Lilly). All 3 of these agents when combined with hormone therapy have achieved significant improvements in PFS in first-line and later settings, with remarkably similar HRs. MONALEESA-3 demonstrated for the first time that PFS is improved in the first-line setting when ribociclib is combined with fulvestrant, allowing further flexibility of treatment. We now know that the efficacy of this class of agents is independent of hormone receptor or menopausal status. Differentiation is more difficult. Efficacy is similar but toxicity differs, although only modestly. Ribociclib and palbociclib cause more neutropenia, but without an increase in febrile neutropenia. Abemaciclib causes more diarrhea, which is dose-dependent. Ribociclib is known to prolong the corrected QT interval in a very small number of patients and can cause elevation of liver enzymes without a long-term effect on liver function. The next question is whether we can prevent metastatic disease with CDK4/6 inhibitors. To explore this question, 4 large, randomized phase 3 trials are currently under way.

Doxorubicin or Cisplatin Induction Linked to Good Response to Nivolumab in TNBC

Short-term induction treatment with low-dose doxorubicin or cisplatin may increase the response to nivolumab (Opdivo, Bristol-Myers Squibb) in patients with metastatic triple-negative breast cancer (TNBC), according to a phase 2 study. This finding is important because most patients with TNBC do not respond to checkpoint inhibitors, so strategies to boost response are needed.

The TONIC trial (Nivolumab After Induction Treatment in Triple-Negative Breast Cancer Patients), presented by Dr Marleen Kok of the Netherlands Cancer Institute in Amsterdam, the Netherlands, consisted of 2 stages. In the first stage, 66 patients with metastatic TNBC who had received no more than 3 lines of palliative chemotherapy were randomly assigned to 1 of 5 induction regimens for 2 weeks: (1) irradiation of 1 metastatic lesion, (2) doxorubicin, (3) cyclophosphamide, (4) cisplatin, or (5) no treatment. After this induction period, patients received nivolumab until disease progression. In stage 2, patients continued to be accrued into the induction treatments with the best response (response in at least 30% of patients).

After a median follow-up of 13.4 months, the rate of response to nivolumab was highest in the doxorubicin group (ORR, 35%) and second-highest in the cisplatin group (ORR, 23%). Biopsy samples taken after 3 cycles of nivolumab in the doxorubicin and cisplatin groups revealed an upregulation in gene signatures associated with improved response to anti–programmed death 1 agents, and an increase in T cells and T-cell clonality.

Dr Kok said that the observed clinical responses in TONIC, together with the translational data, suggest that "induction with doxorubicin or cisplatin may result in an increased likelihood of response to nivolumab, upregulation of gene signatures associated with response to anti–programmed death 1, and increases in T cells and clonality of the T cells." She said that the doxorubicin induction cohort and probably the cisplatin induction cohort will be expanded in stage 2 of the trial.

Kok M, Voorwerk L, Horlings H, et al. Adaptive phase II randomized trial of nivolumab after induction treatment in triple negative breast cancer (TONIC trial): final response data stage I and first translational data [ASCO abstract 1012]. *J Clin Oncol*. 2018;36(15)(suppl).

Commentary: The results of this intriguing trial support the concept of immune "induction," or enhancement of the host antitumor immune response, as a way to increase overall response to checkpoint inhibition. In TONIC, patients received a very brief induction over a 2-week period, then continued the checkpoint inhibitor alone. Both the doxorubicin and cisplatin arms had impressive response rates. However, this is a small, hypothesis-generating trial, and results must be interpreted with caution, given the known 23% to 25% response rate to checkpoint inhibition alone in the first-line setting for metastatic TNBC and the small number of patients enrolled. Indeed, the initial results of checkpoint inhibition in heavily pretreated TNBC suggested response rates from 18% to 19%, but in larger data sets response rates fell to 5% to 8%. Nonetheless, this exciting and novel approach is now being studied in multiple trial settings, including combinations with chemotherapy, radiation therapy, and immune agonists, in both the metastatic and neoadjuvant settings.

Denosumab Studies Produce Mixed Results in Breast Cancer

The RANKL inhibitor denosumab (Xgeva, Amgen) reduced the risk for fractures and cancer recurrence in patients with breast cancer, according to 2 recent phase 3 trials. The first trial also found an improvement in DFS in postmenopausal breast cancer, whereas the second one found no improvement in DFS in stage 2 or 3 breast cancer.

The first trial, called ABCSG-18 (Study to Determine Treatment Effects of Denosumab in Patients With Breast Cancer Receiving Aromatase Inhibitor Therapy), included 3425 postmenopausal patients with early hormone receptor–positive breast cancer who were receiving an aromatase inhibitor. Michael Gnant of the Medical University of Vienna in Vienna, Austria, and colleagues randomly assigned patients in a 1:1 ratio to receive either denosumab or placebo every 6 months during aromatase inhibitor treatment. Earlier results showed that adjuvant denosumab significantly reduced clinical fractures. Current results, after a median follow-up of 72 months, found that DFS was significantly longer in the denosumab arm than in the placebo arm at 5 years (89.2% vs 87.3%) and at 8 years (80.6% vs 77.5%). Surprisingly, much of this benefit in DFS was caused by a reduction in new primary cancers rather than a reduction in breast cancer recurrences. No osteonecrosis of the jaw was seen, and 1 potential atypical femur fracture occurred in the denosumab arm.

The second trial, called D-CARE (Study of Denosumab as Adjuvant Treatment for Women With High Risk Early Breast Cancer Receiving Neoadjuvant or Adjuvant Therapy), included 4509 patients with high-risk stage II or III nonmetastatic breast cancer. Dr Robert E. Coleman of the University of Sheffield in Sheffield, the United Kingdom, and coinvestigators randomly assigned patients to standard locoregional and adjuvant or neoadjuvant

therapy plus either denosumab or placebo every month for 6 months, then every 3 months for up to 5 years. After a median follow-up of 67 months, denosumab was not associated with any improvements in bone metastasis–free survival, DFS, or overall survival compared with placebo. First recurrence in bone was delayed in patients in the denosumab group, but no overall benefit for distant metastases was noted. As in ABCSG-18, the incidence of fractures was reduced. Osteonecrosis of the jaw occurred in 5.4% of the patients on denosumab and 0.2% of the patients on placebo. Atypical femoral fracture occurred in 0.4% of patients on denosumab.

Gnant M, Pfeiler G, Steger GG, et al. Adjuvant denosumab in early breast cancer: disease-free survival analysis of 3,425 postmenopausal patients in the ABCSG-18 trial [ASCO abstract 500]. *J Clin Oncol*. 2018;36(15)(suppl).

Coleman RE, Finkelstein D, Barrios CH, et al. Adjuvant denosumab in early breast cancer: first results from the international multicenter randomized phase III placebo controlled D-CARE study [ASCO abstract 501]. *J Clin Oncol*. 2018;36(15)(suppl).

Commentary: The results of these 2 trials highlight the importance of both patient and endpoint selection in prospective clinical trials, as well as of understanding how to balance intensity of treatment vs toxicity. The ABCSG-18 trial suggests clinical benefit from adjuvant denosumab as a secondary endpoint in patients with hormone receptor–positive disease who primarily received adjuvant endocrine therapy. However, the D-CARE trial enrolled a very heterogeneous population, including patients with hormone receptor–negative and HER2-positive disease; prescribed an intensive regimen of denosumab; and employed a nonstandard and difficult endpoint in this population—bone metastases–free survival. What we learned from these 2 trials is that denosumab may indeed have a role in reducing metastases in patients with hormone receptor–positive breast cancer receiving aromatase inhibitors, but there is no role for this agent in specifically preventing bone metastases in all types of breast cancer. In addition, dosing more frequently than every 6 months or at doses higher than 60 mg is associated with unacceptable toxicity. It is important to note that in ABCSG-18, 60 mg of denosumab every 6 months during adjuvant aromatase inhibitor therapy significantly reduces fractures—the primary endpoint of this study.

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