Highlights in Breast Cancer From the 2016 American Society of Clinical Oncology Annual Meeting

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Commentary by Hope S. Rugo, MD

Abemaciclib Shows Signs of Efficacy and Tolerability in HR+/HER2– Breast Cancer

The CDK4/6 inhibitor abemaciclib demonstrated efficacy and tolerability in a phase 2 study of women with hormone receptor–positive (HR+), HER2-negative (HER2–) metastatic breast cancer.

For the multicenter, single-arm study, called MONARCH 1 (A Study Of Abemaciclib In Participants With Previously Treated Breast Cancer That Has Spread), Dr Maura N. Dickler of Memorial Sloan Kettering Cancer Center in New York, New York, and colleagues studied 132 patients with HR+/HER2– metastatic breast cancer that had progressed during or after treatment with endocrine therapy and chemotherapy. To be eligible, patients had to have measurable disease, an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1, no metastases to the central nervous system, and 1 or 2 lines of previous chemotherapy in the metastatic setting.

The patients' median age was 58 years. Of the 132 patients, 44.7% had an ECOG performance status score of 0 or 1, 90.2% had visceral disease, and 50.8% had 3 or more sites of metastasis. Patients received 200 mg of oral abemaciclib every 12 hours until unacceptable toxicity or disease progression occurred.

Results at 12 months revealed a complete response rate of 0% and a partial response rate of 19.7%. The rate of stable disease at 6 or more months was 22.7%, making the clinical benefit rate 42.4%. Among patients who responded, the median time to response was 3.7 months and the median duration of response was 8.6 months. Median progression-free survival (PFS) was 6.0 months, and median overall survival (OS) was 17.7 months.

The most common adverse events related to treatment were diarrhea, fatigue, nausea, decreased appetite, and abdominal pain. Grade 3 diarrhea occurred in 19.7% of patients, and grade 3 fatigue occurred in 12.9% of patients. High-grade neutropenia was uncommon, with grade 3 neutropenia occurring in 22.3% of patients and grade 4 neutropenia in 4.6% of patients. Febrile neutropenia developed in 1 patient during the 30-day follow-up. An elevation in creatinine developed in nearly all patients, but this was not felt to be a clinically significant elevation because the glomerular filtration rate was not increased.

Although nearly half of the patients (49.2%) required a reduction in dose, few patients (7.7%) discontinued abemaciclib because of adverse events. "Overall, abemaciclib was well tolerated in this late-line population," said Dr Dickler.

Studies have shown that fewer than 1 in 5 women with HR+/HER2– breast cancer that is refractory to endocrine therapy, or who have symptomatic visceral disease, respond to chemotherapy. Therefore, the need for novel agents to treat these patients is great. Dr Dickler said that two phase 3 studies of abemaciclib in combination with endocrine therapy—MONARCH 2 and MONARCH 3—are ongoing.

Dickler MN, Tolaney SM, Rugo HS, et al. MONARCH1: results from a phase II study of abemaciclib, a CDK4 and CDK6 inhibitor, as monotherapy, in patients with HR+/HER2- breast cancer, after chemotherapy for advanced disease [ASCO abstract 510]. *J Clin Oncol*. 2016;34(15)(suppl).

Commentary: Over the last 2 years, we have seen very encouraging data on the combination of the CDK4/6 inhibitor palbociclib with hormone therapy in the first-line and later-line settings, with clinically significant improvements in PFS. Abemaciclib is a unique agent in that it is 14-fold more potent at inhibiting CDK4 than CDK6. MONARCH 1 confirmed that abemaciclib is the only CDK4/6 inhibitor with durable single-agent activity in hormone-refractory HR+ breast cancer, with a different but manageable toxicity profile compared with palbociclib. We await the data on hormone combinations with great interest.

Analysis Supports Use of Anthracyclines in High-Risk Breast Cancer

An interim analysis of 3 trials does not support the omission of anthracyclines from chemotherapy for women with high-risk, early-stage breast cancer, according to a recent study. The fact that anthracyclines were introduced before taxanes has made it difficult to determine whether anthracyclines provide additional benefit to women taking cyclophosphamide plus a taxane.

In order to learn more about the role of anthracyclines, Dr Joanne L. Blum of US Oncology Research (USOR) and Texas Oncology in Dallas, Texas, and colleagues examined data from 3 sequential clinical trials that randomly assigned women with high-risk, early-stage,

HER– breast cancer to receive 6 cycles of docetaxel/cyclophosphamide (TC) or a standard taxane/doxorubicin/cyclophosphamide regimen (TaxAC). The trials, collectively known as the ABC (Anthracyclines in Early Breast Cancer) adjuvant trials, were developed by USOR and the National Surgical Adjuvant Breast and Bowel Project. The analysis included a total of 4156 women, of whom 2094 received TC and 2062 received TaxAC.

The primary goal of the ABC study was to determine whether invasive disease–free survival (IDFS) with TC was noninferior compared with TaxAC, as defined by a hazard ratio (HR) of less than 1.18. After a median of 3.2 years, when the pre-specified number of IDFS events had been reached, the HR was found to be 1.20.

Based on the 399 IDFS events at the interim cutoff, the 4-year IDFS was significantly higher with TaxAC than with TC: 90.7% vs 88.2%. When looking at IDFS by hormone and nodal status, the researchers found that TaxAC provided minimal or no benefit in HR+, node-negative patients, a small benefit in HR+ patients with 1 to 3 positive nodes or HR– patients with negative nodes, and a large benefit in patients with HR+ disease and 4 or more positive nodes or those with HR– disease and positive nodes.

More locoregional and distant IDFS events occurred in the TC arm than in the TaxAC arm. In a finding that Dr Blum described as "striking," leukemia developed in 5 patients in the TaxAC arm and no patients in the TC arm. The 4-year OS was high in both groups and did not differ significantly between the 2 arms: 94.7% with TC vs 95.0% with TaxAC.

"Additional follow-up and correlative studies to identify biomarkers of anthracycline benefit will be crucial for fully determining the utility of anthracyclines across this heterogeneous patient population," Dr Blum concluded.

Blum JL, Flynn PJ, Yothers G, et al. Joint analysis of the ABC (Anthracyclines in Early Breast Cancer) trials (USOR 06-090, NSABP B-46I/USOR 07132, NSABP B-49 [NRG Oncology]) comparing docetaxel plus cyclophosphamide (TC) to anthracycline/taxane-based chemotherapy regimens (TaxAC) in women with high-risk, HER2-negative breast cancer [ASCO abstract 1000]. *J Clin Oncol.* 2016;34(15)(suppl).

Commentary: The long-awaited data from the ABC trials leads us to several very important conclusions regarding adjuvant therapy in early-stage breast cancer. An anthracycline-containing regimen is superior to a non–anthracycline-containing regimen in patients with triple-negative breast cancer, with numerically improved DFS that is magnified in patients with higher-risk cancers, as indicated by node positivity. For HR+ disease, the overall benefit from chemotherapy is much smaller. In this study, it is likely that few patients with HR+, node-negative disease (or even those with 1-3 positive nodes) benefitted much from chemotherapy, and certainly there was no benefit from the use of an anthracycline. For those with 4 or more positive nodes and HR+ disease, these data suggest that an anthracycline-containing regimen is superior to 6 cycles of TC. These data do not tell us anything about the relative benefit of 6 vs the previously studied 4 cycles of TC; inference from previous studies suggests that there is unlikely to be much difference. In the end, the decision is all about weighing risk vs benefit; OS was excellent across both arms.

Standard Regimen Produces Better Response, Worse Safety Than T-DM1

A standard combination of chemotherapy and HER2-blocking agents produced a higher pathologic complete response (pCR) rate than did dual HER2 blockade with trastuzumab emtansine (T-DM1; Kadcyla, Genentech) and pertuzumab (Perjeta, Genentech) in a trial of patients with HER2+ early breast cancer. The safety profile of the T-DM1 regimen was better, however, and health-related quality of life and physical function were maintained longer.

Dr Sara A. Hurvitz, of the UCLA Jonsson Comprehensive Cancer Center in Los Angeles, California, presented the results of the trial, called KRISTINE. The trial enrolled 444 women who had HER2+ early breast cancer with tumors larger than 2 cm. Patients were randomly assigned to 6 cycles of neoadjuvant treatment either with docetaxel, carboplatin, trastuzumab (Herceptin, Genentech), and pertuzumab (TCHP) or with T-DM1 plus pertuzumab (KP). After surgery, patients in the TCHP group received trastuzumab plus pertuzumab and those in the KP group received T-DM1 plus pertuzumab for 12 cycles. Patients in the KP group who had significant residual disease at the time of surgery were encouraged to undergo standard postoperative chemotherapy before beginning maintenance therapy. More than 60% of the women had HR+ breast cancer.

Dr Hurvitz and her colleagues found that the pCR rate in the breast and lymph nodes was significantly higher in the TCHP arm than in the KP arm (56% vs 44%). The difference between the TCHP and KP arms was especially pronounced among women with HR– breast cancers (73% vs 54%), but was not statistically significant among women with HR+ breast cancers (44% vs 35%). In addition, breast-conserving surgery was significantly more common among women in the TCHP arm than in the KP arm (53% vs 42%).

Health-related quality of life and physical functioning were maintained for significantly longer with KP than with TCHP (HR, 0.60 vs 0.47). The rates of adverse events, serious adverse events, grade 3 or 4 adverse events, and adverse events leading to treatment discontinuation of any component were all higher with TCHP than with KP (98.6% vs 88.3%, 28.8% vs 4.9%, 64.4% vs 13.0%, and 8.7% vs 3.1%, respectively).

"As expected, febrile neutropenia, neutropenia, diarrhea, and cytopenias were more common" with TCHP than with KP, said Dr Hurvitz.

Dr Hurvitz said that biomarker data and long-term follow-up from this study will be reported at a future date. Other studies are also evaluating the use of T-DM1 in early-stage breast cancer: KATHERINE and KAITLIN.

Hurvitz SA, Martin M, Symmans WF, et al. Pathologic complete response (pCR) rates after neoadjuvant trastuzumab emtansine (T-DM1 [K]) + pertuzumab (P) vs docetaxel + carboplatin + trastuzumab + P (TCHP) treatment in patients with HER2-positive (HER2+) early breast cancer (EBC) (KRISTINE) [ASCO abstract 500]. *J Clin Oncol.* 2016;34(15)(suppl).

Commentary: Newer and less toxic therapy is not always better than standard treatment. It is hard to match the marked efficacy, as measured by pCR, of TP-containing taxane-based regimens in early-stage HER2+ breast cancer. However, neoadjuvant trials generally treat patients with relatively higher-risk disease, as measured by tumor burden, and differences in pCR rates have not correlated well with DFS. We have learned that it is unlikely that the addition of pertuzumab adds much to T-DM1. However, T-DM1 may be beneficial as adjuvant therapy in patients with lower-risk disease (eg, the ATEMPT trial). T-DM1 also is being studied in patients who have a higher risk of recurrence based on residual disease after neoadjuvant therapy. We still have a lot to learn, and further analysis of biomarkers to understand both response and resistance is critical as we optimize efficacy balanced against toxicity in HER2+ disease.

Heritage Study Confirms Safety and Efficacy of Trastuzumab Biosimilar

A new study has confirmed that the agent MYL-1401O, a proposed biosimilar for trastuzumab, is as safe and effective as Genentech's Herceptin in patients with HER2+ breast cancer.

"We really feel our results will change the treatment of patients with HER2+ breast cancer worldwide," said Dr Hope S. Rugo of the UCSF Helen Diller Family Comprehensive Cancer Center in San Francisco, California, who presented the results of the study.

Heritage (A Phase III Safety and Efficacy Trial of the Proposed Trastuzumab Biosimilar MYL-1401O Versus Herceptin) is a double-blind study that enrolled 458 patients with HER2+ metastatic breast cancer who had not received chemotherapy or an HER2-targeted agent. Patients were randomly assigned to receive MYL-1401O or Herceptin in combination with a taxane. Those whose disease responded to treatment or stabilized after 8 cycles were able to stop taking the taxane and continue with their HER2-targeted agent.

After 24 weeks of treatment, the overall response rate was "equivalent between the arms," at 69.6% in the MYL-1401O group and 64.0% in the Herceptin group. There also was no significant difference in PFS between the groups. PFS will be analyzed again at 48 weeks.

The rates of serious adverse events, which included neutropenia, febrile neutropenia, leukopenia, and pneumonia, did not differ significantly between the 2 groups, and the events were largely attributed to chemotherapy. The rates of fatal adverse events also were similar between the 2 groups; 4 patients in each group died, and these deaths were "all due to treatment-related characteristics or disease, and not felt to be related to the specific HER2-targeted agent." The 2 groups also did not differ in left ventricular ejection fraction.

Immunogenicity was low in both groups, with anti-drug antibodies detected in 2.4% of patients in the MYL-1401O group and 2.8% of patients in the Herceptin group. The trough (C_{min}) concentrations were comparable between the 2 groups at week 15, as were the maximum (C_{max}) concentrations and areas under the curve.

Dr Rugo concluded that Heritage demonstrated equivalent efficacy of MYL-1401O and Herceptin in combination with a taxane as first-line therapy for HER2+ metastatic breast cancer at 24 weeks, with similar safety, immunogenicity, and pharmacokinetics. She said that "MYL-1401O has the potential to meet the need for an affordable treatment option for patients with HER2+ cancers."

Biosimilars are agents that are highly similar to biologic agents, which are complex proteins with a high molecular weight. They generally are more difficult to develop than generic versions of traditional small-molecule agents.

Rugo HS, Barve A, Watter CF, et al. Heritage: a phase III safety and efficacy trial of the proposed trastuzumab biosimilar MYL-1401O versus Herceptin [ASCO abstract LBA503]. *J Clin Oncol.* 2016;34(15)(suppl).

Commentary: Complex therapeutic agents have changed outcomes for a number of common cancers. Most notably, the addition of trastuzumab to therapy for both early-stage and late-stage breast cancers has markedly improved survival. Unfortunately, many

patients around the world have limited access to trastuzumab owing to its cost. With the patent expired or expiring soon, there has been great interest in the development of "biosimilars" in order to reduce cost and potentially improve access. MYL-1401O is a proposed trastuzumab biosimilar that has met chemical, pharmacokinetic, and efficacy endpoints for biosimilarity. This represents an exciting step in the goal to provide wider access to this lifesaving antibody. Other biosimilars are in development in oncology. Of note, researchers presented data at this meeting on a proposed biosimilar for bevacizumab that demonstrated efficacy similar to that of Genentech's Avastin in non-small cell lung cancer.

OPT-822 Vaccine Improves Progression-Free Survival in a Subset of Patients, but Not Overall

A phase 2/3 trial revealed that the OPT-822 vaccine did not improve PFS better than a placebo injection vaccine in women with metastatic breast cancer. PFS did improve, however, among the patients who mounted an immune response to the vaccine.

The OPT-822 vaccine consists of globo H, covalently linked to the carrier protein KLH (keyhole limpet hemocyanin), and a saponin-based adjuvant. Globo H is a carbohydrate antigen that is highly expressed in breast cancer.

In the phase 2/3 double-blind trial, which was presented by Dr Rugo, 349 women with metastatic breast cancer were randomly assigned 2:1 to receive cyclophosphamide plus either the vaccine or a placebo injection. To be eligible, the women had to have achieved a complete response, a partial response, or stable disease following at least 1 line of chemotherapy or hormone therapy. Patients could not have had more than 2 progressive disease events in the metastatic setting. The vaccine was administered once a week for the first 3 weeks, then monthly, and then as a booster at 37 weeks. Globo H expression was measured in approximately 70% of the patients.

After a median follow-up of up to 22.5 months, no statistically significant difference in median PFS was observed between the vaccine arm and the placebo arm (32.9 vs 40.0 weeks). There was a trend toward improved PFS among the patients who received all 9 injections of the vaccine, but this difference was not statistically significant.

Among the 50% of patients who had an immune response to the vaccine, however—defined as a titer of at least 1:160 against globo H—PFS was significantly higher than in the nonresponder group (HR, 0.51) and the placebo group (HR, 0.71). People who were treated with the vaccine but did not mount a globo H–specific immune response had a worse median PFS than those in the placebo group (HR, 1.38), "suggesting that patients who were treated with the vaccine who did not mount a globo H–specific response have a particularly bad prognosis."

An interim analysis of OS revealed that patients who received the vaccine but did not respond to it had a worse OS than did those in the placebo group (HR, 1.11). The researchers were unable to identify any measures of tumor biological subtype or levels of globo H expression that predicted whether patients were more or less likely to respond to treatment.

The vaccine therapy was well tolerated, with the most common side effects being grade 1 or 2 pyrexia and injection site reactions.

Dr Rugo concluded that future studies should explore the amplification of immune response and tumor-specific effects, potentially with combination therapy.

Huang CS, Yu AL, Tseng LM, et al. Randomized phase II/III trial of active immunotherapy with OPT-822/OPT-821 in patients with metastatic breast cancer [ASCO abstract 1003]. *J Clin Oncol.* 2016;34(15)(suppl).

Commentary: Vaccines for the treatment of cancer have been of great interest for decades, ever since the recognition that the host's immune system is unable to generate an appropriate response because it does not recognize the cancer as foreign. The failure of vaccines has been related to difficulties in identifying targets and assessing efficacy, and the inability of immunosuppressed patients to generate an immune response. As we gather data on checkpoint inhibitors, we are gaining a greater understanding of the factors that are important in mounting an effective immune response. The intriguing data on the OPT-822 vaccine suggest that amplification of the immune response might improve the efficacy of this vaccine, therefore improving patient outcomes, and that the generation of an immune response to the vaccine should be a focal endpoint for the next series of trials.

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