Highlights in Breast Cancer From the 2017 American Society of Clinical Oncology Annual Meeting

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Commentary by Hope S. Rugo, MD

Subset of Patients With Heavily Pretreated Metastatic TNBC Respond to Pembrolizumab

A subset of patients with heavily pretreated metastatic triple-negative breast cancer (mTNBC) respond to pembrolizumab (Keytruda, Merck) monotherapy, according to a study presented by Dr Sylvia Adams of the New York University School of Medicine in New York, New York. The response rate appeared to be the same in patients whose tumors expressed programmed death ligand 1 (PD-L1) as in those whose tumors did not.

Cohort A of the phase 2 KEYNOTE-086 study (Study of Pembrolizumab Monotherapy for Metastatic Triple-Negative Breast Cancer) enrolled 170 women (median age, 54 years) with centrally confirmed mTNBC who had disease progression, at least 1 prior systemic treatment for mTNBC, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and no radiographic evidence of central nervous system (CNS) metastases. More than one-third of patients (44%) had received at least 3 prior lines of treatment for metastatic disease, 51% had elevated lactate dehydrogenase (LDH), 74% had visceral metastases, and 62% had PD-L1–positive tumors.

The patients received 200 mg of pembrolizumab every 3 weeks for 2 years or until disease progression, intolerable toxicity, or withdrawal. Tumors were imaged every 9 weeks for the first year and every 12 weeks thereafter.

After a median follow-up of 11 months, 9 patients (5%) were still taking pembrolizumab. Treatment-related adverse events (TRAEs) of any grade occurred in 60% of patients, and those of grade 3 or 4 occurred in 12% of patients. TRAEs led to discontinuation of pembrolizumab in 4% of patients but did not cause any deaths.

The objective response rate (ORR) to pembrolizumab was approximately the same in PD-L1–positive patients (5%; 95% CI, 2%-11%) as in PD-L1–negative patients (5%; 95% CI, 1%-13%). The best overall response was a complete response (CR) in 1% of patients, a partial response (PR) in 4%, stable disease (SD) in 21%, and not evaluable in 3%. The disease control rate was 8%, and the median duration of response was 6 months. Median progression-free survival (PFS) was 2 months, and median overall survival (OS) was 9 months. Patients who had poor prognostic factors, such as high LDH and liver or visceral metastases, had a trend toward a reduced ORR.

Dr Adams said that KEYNOTE-086, which is "so far the largest immunotherapy study for metastatic triple-negative breast cancer," showed that pembrolizumab monotherapy produced durable antitumor activity in a subset of patients with heavily pretreated mTNBC. "The activity appeared independent of PD-L1 expression, and the overall response was numerically lower in women who had poor prognostic features." Patients who achieved a CR, PR, or SD had "promising" survival, whereas patients with poor prognostic factors had a trend toward a worse ORR. Dr Adams also pointed out that the treatment was well tolerated.

She said that analyses of additional biomarkers, such as tumor-infiltrating lymphocytes (TILs), are ongoing. In addition, randomized studies are continuing to examine pembrolizumab as monotherapy and as part of combination therapy for TNBC.

Adams S, Schmid P, Rugo HS, et al. Phase 2 study of pembrolizumab (pembro) monotherapy for previously treated metastatic triple-negative breast cancer (mTNBC): KEYNOTE-086 cohort A [ASCO abstract 1008]. *J Clin Oncol.* 2017;35(15)(suppl).

Pembrolizumab Shows Promise as First-Line Therapy for PD-L1–Positive TNBC

Pembrolizumab monotherapy has a manageable safety profile and promising antitumor activity when used as first-line therapy in PD-L1–positive mTNBC, according to preliminary results from cohort B of the KEYNOTE-086 study. The standard first-line treatment option for mTNBC is chemotherapy, which has poor outcomes in these patients.

The study enrolled patients with centrally confirmed mTNBC who had no prior systemic therapy for metastatic disease, an ECOG performance status of 0 or 1, and no

radiographic evidence of CNS metastases. As in cohort A, patients received 200 mg of pembrolizumab every 3 weeks for 2 years or until disease progression, intolerable toxicity, or withdrawal. Tumors were imaged every 9 weeks for the first year and every 12 weeks thereafter.

Dr Adams presented a poster based on results from the first 52 of 79 enrolled patients (median age, 53 years). Of these patients, 40% had elevated LDH, 69% had visceral metastases, and 87% had received prior adjuvant or neoadjuvant treatment.

After a median follow-up of 7 months, 15 patients (29%) were still taking pembrolizumab. TRAEs of any grade occurred in 71% of patients, and those of grade 3 or 4 occurred in 8% of patients. The most common TRAEs were fatigue, nausea, and diarrhea. TRAEs did not lead to discontinuation of pembrolizumab or death in any patients.

The ORR to treatment was 23%, with the best overall response being CR in 4% of patients, PR in 19%, SD in 17%, and not assessed in 2%. The median time to response was 9 weeks, and the median duration of response was 8 months. The median PFS was 2 months, and the estimated 6-month PFS rate was 29%.

The investigators concluded that based on the early results of this study, pembrolizumab has promising antitumor activity as first-line treatment in patients with PD-L1–positive mTNBC and appears to be well tolerated.

An additional trial, KEYNOTE-355, is examining the use of chemotherapy with or without pembrolizumab in patients with previously untreated, locally recurrent inoperable or metastatic TNBC (NCT02819518).

Adams S, Loi S, Toppmeyer D, et al. Phase 2 study of pembrolizumab as first-line therapy for PD-L1–positive metastatic triple-negative breast cancer (mTNBC): preliminary data from KEYNOTE-086 cohort B [ASCO abstract 1088]. *J Clin Oncol*. 2017;35(15)(suppl).

Pembrolizumab Improves Response to Chemotherapy in HER2-Negative Breast Cancer

The addition of pembrolizumab to standard neoadjuvant therapy improved the rate of pathologic CR in patients with breast cancer that was negative for human epidermal growth factor receptor 2 (HER2), according to a phase 2 study presented by Dr Rita Nanda of the University of Chicago in Illinois. Pembrolizumab was especially effective in TNBC.

As part of the multiple-arm I-SPY 2 trial (Neoadjuvant and Personalized Adaptive Novel Agents to Treat Breast Cancer), 249 patients (median age, 47 to 50 years) with HER2-negative tumors that were at least 2.5 cm across were randomly assigned with adaptive randomization to receive either 200 mg of pembrolizumab or a placebo every 3 weeks in addition to weekly paclitaxel for 12 weeks. This was followed by 4 cycles of doxorubicin/cyclophosphamide, and finally surgery.

The researchers found that the estimated pathologic complete response (pCR) rate was significantly higher in the pembrolizumab group (0.46; 95% CI, 0.34-0.58) than in the control group (0.16; 95% CI, 0.06-0.27). Pembrolizumab was especially effective vs placebo among women with TNBC, tripling the estimated pCR rate (0.60; 95% CI, 0.43-0.78 vs 0.20; 95% CI, 0.06-0.33), but was also effective in women whose tumors were hormone receptor–positive.

Pembrolizumab did not increase the rate of febrile neutropenia, neutropenia without fever, or anemia compared with placebo, although there was a small increase in the rate of grade 3 and higher fatigue and nausea. As expected, there was an elevated risk for hypothyroidism (9%), hyperthyroidism (4%), adrenal insufficiency (9%), and pruritus (25%) with pembrolizumab. In response to the observed toxicities, the investigators added regular measurement of cortisol levels to the study protocol; participants also receive regular thyroid function testing.

Dr Nanda said that a new experimental arm of I-SPY 2, which will begin enrollment soon, will continue the use of pembrolizumab during anthracycline administration.

Nanda R, Liu MC, Yau C, et al. Pembrolizumab plus standard neoadjuvant therapy for high-risk breast cancer (BC): results from I-SPY 2 [ASCO abstract 506]. *J Clin Oncol*. 2017;35(15)(suppl).

Commentary: Immunotherapy is clearly moving forward in breast cancer, as we learn more about the unique characteristics that support response in this characteristically less-immunogenic disease. Prior data have demonstrated better response rates in breast cancers with a higher level of TILs, and increases in both PD-L1 expression and level of TILs in patients with triple-negative and HER2-positive disease vs those who have hormone receptor–positive disease.

Two phase 1b trials demonstrating response rates of 18.5% to 19% to the checkpoint inhibitors pembrolizumab and atezolizumab (Tecentriq, Genentech) in patients with pretreated TNBC generated great excitement regarding the potential for these agents in the treatment of breast cancer. A subsequent larger trial (JAVELIN Solid Tumor; Avelumab in Metastatic or Locally Advanced Solid Tumors) with avelumab (Bavencio, EMD Serono/Pfizer) suggested that the true response rates were much lower (<10%). At the American Association for Cancer Research meeting earlier this year, Dr Peter Schmid of St Bartholomew's Hospital and Barts Cancer Institute in London, United Kingdom, presented data from a large dose-expansion trial of atezolizumab in 112 evaluable patients. This trial

demonstrated an ORR of 10%, which ranged from 4% to 8% in the second-line and third-line settings to 26% in the 19 patients treated in the first-line setting. There was a suggestion that response was greater in those patients whose tumors more highly expressed PD-L1 (the ORR was 13% among those with an immunocytochemistry (IC) score of 2/3+ [71 patients] vs 5% among those with an IC score of 0/1+ [37 patients]). Median PFS was less than 2 months, but median duration of response was 21 months.

The data from KEYNOTE-086 demonstrate similar results in a larger phase 2 trial, with an ORR in the second-line and later patients of 5% vs an impressive 23% in the first-line population. Interestingly, response did not correlate with PD-L1 expression. Toxicity was similar across the trials, and the long duration of disease control in responders was encouraging.

These studies are also supported by data from Luen and colleagues (*Lancet Oncol*. 2017;18(1):52-62) demonstrating reduced tumor T-cell infiltration as tumors progress from early-stage to late-stage disease, suggesting that immune "exhaustion" may be a mechanism of resistance that increases over the disease course. Altogether, this suggests that the success of immunotherapy is likely to be much greater in early-stage disease and early in the metastatic setting. However, response rates of just over 20% are not ideal. Ample evidence has shown that chemotherapy can act as an immune agonist, stimulating the host immune response and ideally creating an environment in which checkpoint inhibitors have greater efficacy.

I-SPY 2 is an adaptively randomized multiple-arm phase 2 neoadjuvant trial in high-risk breast cancer. In the pembrolizumab arm, weekly paclitaxel for 12 doses was given with pembrolizumab for 4 doses, followed by doxorubicin/cyclophosphamide for 4 cycles before surgery. The exciting data presented by Dr Rita Nanda on behalf of the I-SPY 2 investigators indicated a tripling of estimated pCR rates in the triple-negative population and a near-tripling in the hormone receptor–positive, MammaPrint high-risk group. Correlative studies are ongoing to identify the specific characteristics that predict response. Pembrolizumab showed an unexpectedly high rate of adrenal insufficiency up to 3 months after the final pembrolizumab infusion, although all patients were treated and proceeded to surgery. It may be that chemotherapy with specific agents after checkpoint inhibition stimulates a greater host immune response. This has not been reported in other trials and will be studied further in the next arm of I-SPY 2, in which pembrolizumab will continue through doxorubicin/cyclophosphamide for a total of 8 doses. Several trials in the metastatic setting are evaluating checkpoint inhibition with chemotherapy as first-line treatment, and other combination studies with immune agonists are under way.

Olaparib Improves PFS in *BRCA*-Mutated Metastatic Breast Cancer

Olaparib (Lynparza, AstraZeneca) monotherapy improved PFS compared with standard chemotherapy in patients with HER2-negative metastatic breast cancer who have a germline *BRCA* mutation, according to results from the OlympiAD trial (Assessment of the Efficacy and Safety of Olaparib Monotherapy Versus Physicians Choice Chemotherapy in the Treatment of Metastatic Breast Cancer Patients With Germline BRCA1/2 Mutations). Olaparib is an inhibitor of poly(ADP-ribose) polymerase (PARP).

"OlympiAD is the first phase 3 study in metastatic breast cancer demonstrating a benefit for a PARP inhibitor over an active comparator," said presenter Dr Mark E. Robson of the Memorial Sloan Kettering Cancer Center in New York, New York.

Dr Robson and colleagues enrolled 302 adults (median age, 44 years) with HER2-negative metastatic breast cancer and a germline *BRCA* mutation. Patients needed to have received at least 2 prior lines of chemotherapy in the metastatic setting to be eligible. Tumors were triple-negative in half the patients and hormone receptor–positive in the other half. More than two-thirds of the patients (71%) had received prior chemotherapy for metastatic disease, including 29% who had received prior platinum treatment.

Patients were randomly assigned 2:1 to either 300 mg of olaparib tablets twice a day or standard single-agent chemotherapy with capecitabine, vinorelbine, or eribulin (Halaven, Eisai) at the physician's discretion. Treatment continued until progression of disease or unacceptable toxicity.

After 77% maturity of data, PFS was significantly longer in the olaparib group than in the chemotherapy group (7 vs 4 months; hazard ratio [HR], 0.58; 95% CI, 0.43-0.80; *P*=.0009). The time to second progression also was longer in the olaparib group than in the chemotherapy group (13 vs 9 months; HR, 0.57; 95% CI, 0.40-0.83; *P*=.0033). The ORR also was higher with olaparib than with chemotherapy (60% vs 29%).

Adverse events (AEs) of grade 3 or higher occurred in 37% of patients in the olaparib group and 51% of those in the chemotherapy group, with AEs leading to discontinuation in 5% and 8% of patients, respectively. Nausea, anemia, vomiting, fatigue, and neutropenia were the most common AEs with olaparib. Compared with baseline, health-related quality-of-life scores improved by 4 points in the olaparib group and worsened by 4 points in the chemotherapy group, a statistically significant difference.

Dr Robson concluded that PFS and AEs were significantly better with olaparib monotherapy than with chemotherapy in patients with HER2-negative metastatic breast cancer and a germline *BRCA* mutation.

The results also were published in the June 4 issue of the *New England Journal of Medicine*.

Robson ME, Im SA, Senkus E, et al. OlympiAD: phase III trial of olaparib monotherapy versus chemotherapy for patients (pts) with HER2-negative metastatic breast cancer (mBC) and a germline *BRCA* mutation (gBRCAm) [ASCO abstract LBA4]. *J Clin Oncol*. 2017;35(15)(suppl).

Commentary: We have waited with bated breath for the first results of this phase 3 trial of PARP inhibition in breast cancer. The OlympiAD trial enrolled patients with germline mutations in *BRCA1/2* and demonstrated that single-agent PARP inhibition with olaparib was both better tolerated and more effective that a menu of standard chemotherapy options. This has finally paved the path for regulatory approval of a PARP inhibitor for the treatment of breast cancers associated with *BRCA* mutations. OlympiAD used a different formulation of olaparib than is currently available on the market, at a dose of 300 mg twice a day rather than the dose of 400 mg twice a day that is approved for ovarian cancer.

Although OlympiAD met its primary endpoint of improved PFS, what is particularly striking is the marked improvement in response rates vs the relatively modest benefit in PFS. This differential between response and PFS suggests rapid development of resistance to PARP inhibition, at least in the metastatic setting. As we move forward, there are a number of important directions for study. The OlympiA trial (Olaparib as Adjuvant Treatment in Patients With Germline BRCA Mutated High Risk HER2 Negative Primary Breast Cancer) of adjuvant therapy will help us to understand the potential value of PARP inhibition in early-stage breast cancer, perhaps a setting in which development of resistance is less of a barrier to efficacy. In addition, preclinical studies have suggested potential interactions between PARP inhibitors and checkpoint inhibitors; clinical studies are ongoing with this and other combinations. Lastly, we should see data from the phase 3 EMBRACA study (A Study Evaluating Talazoparib, a PARP Inhibitor, in Advanced and/or Metastatic Breast Cancer Patients With BRCA Mutation) in the next year, which is evaluating the PARP inhibitor talazoparib vs treatment of physician choice in patients with *BRCA* mutation–associated metastatic breast cancer.

In sporadic TNBC, there has long been an interest in identifying tumors associated with DNA repair deficiency. Several studies have failed to show benefit from adding the PARP inhibitor veliparib to a taxane/carboplatin backbone, including the recent phase 3 neoadjuvant BrighTNess trial (A Study Evaluating Safety and Efficacy of the Addition of ABT-888 Plus Carboplatin Versus the Addition of Carboplatin to Standard Chemotherapy Versus Standard Chemotherapy in Subjects With Early Stage Triple Negative Breast Cancer), and the TNT trial (Triple Negative Breast Cancer Trial) in patients with metastatic disease could not identify a subset of sporadic TNBC that benefited more from carboplatin than from docetaxel. Certainly the dose and type of PARP inhibitor may make a difference, and assays evaluating DNA repair defects may be more useful in early-stage disease than in advanced-stage disease, where multiple mutations could complicate this evaluation. It is hoped that ongoing and future studies will clarify these issues.

Neoadjuvant Chemotherapy Makes Breast-Conserving Therapy Possible in More Than Half of Women With TNBC

The use of neoadjuvant chemotherapy in women with TNBC that is ineligible for breast-conserving therapy (BCT) makes BCT possible in more than half of cases, according to a new phase 3 study. Many of the women who became eligible for BCT did not elect to have it, however.

Dr Mehra Golshan of the Brigham and Women's Hospital and Dana-Farber Cancer Institute in Boston, Massachusetts, presented the results of the BrighTNess study as a poster.

Dr Golshan and his colleagues randomly assigned women with operable stage II or III TNBC to 1 of 3 neoadjuvant chemotherapy regimens in a 2:1:1 ratio: veliparib/carboplatin/paclitaxel, placebo/carboplatin/paclitaxel, or placebo/paclitaxel. All regimens were followed by doxorubicin/cyclophosphamide.

A total of 604 women (median age, 51 years) underwent surgery, and complete surgical data were available for 599 of these patients. The use of neoadjuvant chemotherapy boosted overall eligibility for BCT from 76% to 84%. Of those eligible for BCT, 68% opted for this procedure over mastectomy.

The rates of pCR did not differ between patients who had BCT (55%) and those who had mastectomy (53%). Patients treated in North America, however, were less likely to choose BCT (55%) than those in Europe and Asia (80%). North American women who underwent mastectomy also were 4 times more likely than their counterparts in Europe and Asia to undergo contralateral prophylactic mastectomy.

Of the 141 patients who were ineligible for BCT at baseline, 53% became eligible after neoadjuvant chemotherapy. Despite this change, only 56% of the patients who became eligible for BCT opted for it over mastectomy. The rate of pCR was higher for patients who became eligible for BCT (49%) than for those who remained ineligible (36%).

A total of 85 patients had a germline *BRCA* mutation. These patients were less likely than patients without the mutation to choose BCT, even if they were eligible.

Dr Golshan, who pointed out that this is the largest prospective analysis of the impact of neoadjuvant chemotherapy on TNBC, told *Clinical Advances in Hematology & Oncology* that the much higher mastectomy rate in North America among women eligible for BCT "is concerning and merits investigation."

Golshan M, Loibl S, Huober JB, et al. Breast conservation after neoadjuvant chemotherapy for triple-negative breast cancer: surgical results from an international randomized trial (BrighTNess) [ASCO abstract 514]. *J Clin Oncol*. 2017;35(15) (suppl).

Commentary: Many issues affect surgical decisions for a woman with a diagnosis of early-stage breast cancer. Fear of recurrence and future new breast cancers is certainly one driving factor, but difficulty with diagnosis, concerns about the ability of screening to detect new cancers, and the desire to avoid radiation therapy may also impact these decisions. Reconstruction options have certainly improved, but reconstruction can result in complications and the need for additional surgery. It is clear that patient and physician education and awareness of outcomes data are important, given these data. The neoadjuvant treatment period allows time for discussion of options and review of relative risks and benefits that may help to reduce mastectomy rates in patients with an excellent response to therapy.

Addition of Abemaciclib to Fulvestrant Improves Tumor Response in Hormone Receptor–Positive Breast Cancer

The addition of abemaciclib to fulvestrant (Faslodex, AstraZeneca) was shown in a new study to significantly improve PFS and ORR in women with hormone receptor–positive, HER2-negative advanced breast cancer whose disease had progressed on prior endocrine therapy. Abemaciclib is an inhibitor of cyclin-dependent kinase 4 and 6 (CDK4/6).

The study, called MONARCH 2 (A Study of Abemaciclib Combined With Fulvestrant in Women With Hormone Receptor Positive HER2 Negative Breast Cancer), was presented by Dr George W. Sledge Jr of Stanford University in Stanford, California.

The study enrolled 669 women (median age, 59-62 years) with hormone receptor–positive, HER2-negative advanced breast cancer whose disease had progressed on prior adjuvant or neoadjuvant endocrine therapy and who had not received chemotherapy for metastatic breast cancer. Women were randomly assigned 2:1 to receive 150 mg of abemaciclib twice a day plus fulvestrant, or a placebo plus fulvestrant. A total of 56% of patients had visceral disease, 72% had measurable disease, 25% had primary resistance to endocrine therapy, and 82% were postmenopausal. Patients who were premenopausal or perimenopausal received a gonadotropin-releasing hormone agonist.

After a median follow-up of 20 months, the median PFS was significantly higher in the abemaciclib/fulvestrant group than in the placebo/fulvestrant group (16 vs 9 months; HR, 0.553; 95% CI, 0.449-0.681; $P<.0001$). Among patients with measurable disease, the ORR was more than doubled in the abemaciclib/fulvestrant group compared with the placebo/fulvestrant group (48% vs 21%).

The TEAEs that occurred more often in the abemaciclib group were diarrhea, neutropenia, nausea, and fatigue. Diarrhea generally was manageable with dose adjustment and antidiarrheal medication.

Dr Sledge said that based on the results of this study, "the combination of abemaciclib with endocrine therapy will be tested as adjuvant therapy for hormone receptor–positive, HER2-negative, high-risk breast cancer" beginning in the third quarter of 2017.

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

Sledge GW, Toi M, Neven P, et al. MONARCH 2: Abemaciclib in combination with fulvestrant in patients with HR+/HER2- advanced breast cancer who progressed on endocrine therapy [ASCO abstract 1000]. *J Clin Oncol*. 2017;35(15) (suppl).

Commentary: MONARCH 2 is the second study to show a significant benefit in PFS from the addition of a CDK4/6 inhibitor to fulvestrant in patients with previously treated hormone receptor–positive advanced breast cancer. The first such study was PALOMA-3 (Palbociclib Combined With Fulvestrant In Hormone Receptor-Positive HER2-Negative Metastatic Breast Cancer After Endocrine Failure), which studied the CDK4/6 inhibitor palbociclib (Ibrance, Pfizer).

Palbociclib and ribociclib (Kisqali, Novartis) are approved by the US Food and Drug Administration (FDA) in combination with an aromatase inhibitor as first-line therapy of hormone receptor–positive metastatic breast cancer, and palbociclib is approved in combination with fulvestrant. Based on the data from MONARCH 2, with priority review from the FDA, it is expected that abemaciclib will be approved in this setting in the near future.

Abemaciclib has already demonstrated single-agent efficacy in more heavily pretreated patients with hormone receptor–positive disease, with a response rate of 19.5% in the MONARCH 1 study. Unlike palbociclib and ribociclib, which are given on a 3-week-on, 1-week-off schedule, abemaciclib can be dosed continuously. The toxicity profile is also different, with more grade 3 or higher diarrhea and less grade 3 or higher neutropenia with abemaciclib. The diarrhea associated with abemaciclib clearly is dose related, as a dose reduction early in the course of MONARCH 2 reduced this toxicity significantly, and patient education

and early intervention with antidiarrheal therapy are quite effective.

The PFS seen in the experimental arm of MONARCH 2 is the longest described to date in the second-line or later setting with fulvestrant. Of note, MONARCH 2 enrolled a highly hormone-sensitive population, with only 1 prior hormone therapy for advanced disease and no prior chemotherapy, quite different from the population enrolled in PALOMA-3. These very encouraging data provide important new natural history data for our patients and encourage the use of sequential hormone therapy with delayed use of chemotherapy. Abemaciclib has been shown to cross the blood-brain barrier, with preliminary efficacy data presented at ASCO in patients with hormone receptor–positive disease and brain metastases.

As noted earlier, an adjuvant trial is to open later in 2017 with abemaciclib. Two large trials with palbociclib are under way, and 2 trials with ribociclib are just starting to enroll patients. Up to 15,000 women will be enrolled in adjuvant trials evaluating CDK4/6 inhibition in combination with hormone therapy in the next few years. This approach is hoped to reduce distant recurrence and death from the most common subtype of breast cancer.

Pertuzumab Improves Patient Outcomes in HER2-Positive Early Breast Cancer

The addition of pertuzumab (Perjeta, Genentech) to trastuzumab (Herceptin, Genentech) and chemotherapy significantly improves invasive disease–free survival (IDFS) in patients with HER2-positive early breast cancer, according to a new study.

Previous studies had shown that the use of pertuzumab increased PFS and OS in patients with metastatic disease. Pertuzumab has complementary mechanisms of action with trastuzumab.

The study, called APHINITY (Adjuvant Pertuzumab and Herceptin in Initial Therapy), included patients with HER2-positive nonmetastatic breast cancer. As presented by Dr Gunter von Minckwitz of the German Breast Group in Neu-Isenburg, Germany, a total of 4805 patients were randomly assigned to chemotherapy/trastuzumab plus either pertuzumab or a placebo. Disease was node-positive in 63% of patients and hormone receptor–negative in 36% of patients.

A total of 85% of patients in the pertuzumab group and 87% of those in the placebo group completed their treatment. At a median follow-up of 45 months, IDFS events were significantly less common in the pertuzumab group than in the placebo group (7.1% vs 8.7%; HR, 0.81; 95% CI, 0.66-1.00; *P*=.045).

The estimated IDFS at 3 years also was significantly better with pertuzumab than with placebo (94.1% vs 93.2%; HR, 0.82; 95% CI, 0.68-0.99; *P*=.043). This difference was more pronounced among patients in the node-positive subgroup (92.0% vs 90.2%; HR, 0.77; 95% CI, 0.62-0.96; *P*=.019).

The safety profile of pertuzumab was consistent with what previous studies had found. Rates of heart failure or cardiac death were low in both the pertuzumab (0.7%) and placebo (0.3%) groups, as were the rates of an asymptomatic or mildly asymptomatic drop in left ventricular ejection fraction (2.7% vs 2.8%). Grade 3 or higher diarrhea was more frequent with pertuzumab than with placebo (9.9% vs 3.7%).

Dr von Minckwitz said that the study met its primary objective, reducing the risk for an IDFS event by 19% compared with placebo. The node-positive and hormone receptor–negative cohort appeared to derive the most benefit from treatment.

"Continued follow-up is crucial for this study," said Dr von Minckwitz. Follow-up of up to 10 years is planned to examine OS, longer-term IDFS, and safety.

The results also were published online June 4 in the *New England Journal of Medicine*.

von Minckwitz G, Procter M, de Azambuja E, et al. APHINITY trial (BIG 4-11): A randomized comparison of chemotherapy (C) plus trastuzumab (T) plus placebo (Pla) versus chemotherapy plus trastuzumab (T) plus pertuzumab (P) as adjuvant therapy in patients (pts) with HER2-positive early breast cancer (EBC) [ASCO abstract LBA500]. *J Clin Oncol*. 2017;35(15)(suppl).

Commentary: After the truly remarkable improvement in both PFS and OS seen with the addition of pertuzumab to trastuzumab/docetaxel as first-line therapy for largely trastuzumab-naive metastatic HER2-positive breast cancer, the results of the APHINITY trial were disappointing—although they also served to validate the potent impact of trastuzumab in early-stage HER2-positive disease.

APHINITY enrolled almost 5000 women with early-stage HER2-positive breast cancer, 78% of whom received an anthracycline/taxane-based chemotherapy regimen and just over 60% of whom had node-positive disease. Of interest, 64% had hormone receptor–positive disease, perhaps owing to the increased use of neoadjuvant therapy for hormone receptor–negative cancers.

The outcome in the control group—all of whom received chemotherapy and trastuzumab—was better than expected, with an IDFS at 3 years of 93.2% vs a predicted rate of 89.2%. At 4 years, the absolute benefit from the addition of 1 year of pertuzumab was only 1.7% for the entire population, with a 1.1% benefit in the rate of distant recurrence as a first event and a 0.6% difference in distant recurrence-free interval. The impact of pertuzumab on IDFS was clearly risk based. The absolute benefit was 3.2% in node-positive disease vs 0.5% in node-negative disease,

and 2.3% in hormone receptor–negative disease vs 1.4% in hormone receptor–positive disease. Pertuzumab increased grade 3 or greater diarrhea, particularly in patients receiving docetaxel/carboplatin, in whom the rate was 18% (vs 6.1% in the control group). There was no deterioration in health-related quality of life with pertuzumab, however.

How do we implement these data in the clinic? Clearly the addition of pertuzumab benefited patients with the highest risk for HER2-positive disease, including patients with node-positive and particularly hormone receptor–negative disease, who tend to be very responsive to HER2-targeted therapy. Based on the APHINITY data, pertuzumab does not seem to provide benefit for node-negative, HER2-positive breast cancer and cannot be recommended at the current time. Caution should be exercised when pertuzumab is used in combination with docetaxel, carboplatin, and trastuzumab, with careful education about diarrhea risk and management. Unfortunately, the optimal duration of pertuzumab therapy was not addressed in APHINITY. For patients receiving neoadjuvant pertuzumab-based combinations who achieve a pCR, the benefit of continuing pertuzumab to complete 1 year of therapy remains unknown. We look forward to longer follow-up and the extensive translational work that is planned as part of this large international trial. We hope that those results will help to identify patients whose tumors are most likely to benefit from pertuzumab.

Lapatinib Still Does Not Improve Outcomes in HER2-Positive Early Breast Cancer

A combination of lapatinib (Tykerb, Novartis) and trastuzumab is not more effective than trastuzumab alone as adjuvant treatment for women with HER2-positive early breast cancer, according to updated results from the phase 3 ALTTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation) trial. ALTTO was designed to explore whether dual HER2 blockade would improve disease-free survival (DFS) in the adjuvant setting.

Dr Alvaro Moreno-Aspitia of the Mayo Clinic in Jacksonville, Florida, presented the results from a 6.9-year median follow-up; preliminary results from a 4.5-year follow-up were presented at the 2014 ASCO annual meeting and published in the *Journal of Clinical Oncology* in 2015.

In ALTTO, researchers randomly assigned 8381 patients to receive either lapatinib/trastuzumab, trastuzumab followed by lapatinib, trastuzumab alone, or lapatinib alone; the lapatinib-alone arm was halted for futility. At this most recent follow-up, there were 705 disease-free survival (DFS) events for lapatinib/trastuzumab vs trastuzumab alone; the investigators were expecting to see 850 of these events.

As in the earlier results, DFS was not significantly better for lapatinib/trastuzumab than for lapatinib alone (HR, 0.86; 95% CI, 0.74-1.00; *P*=.048). There was a small increase in DFS for lapatinib/trastuzumab vs lapatinib alone among hormone receptor–negative patients vs hormone receptor–positive patients, however (HR, 0.80; 95% CI, 0.64-1.00; *P*=.053). There also was a small increase in DFS with lapatinib/trastuzumab among patients who received sequential chemotherapy.

AEs such as rash, hepatobiliary AEs, and diarrhea were more frequent with lapatinib/trastuzumab (93%) than with trastuzumab alone (64%). Cardiac toxicity was low in all treatment arms.

Dr Moreno-Aspitia said that dual blockade of HER2 had not led to any significant changes in DFS or OS since the earlier results were presented.

"An interesting observation is that HER2-positive, hormone receptor–negative tumors may have a different biological behavior, so patients with this profile may benefit from dual blockade," said Dr Moreno-Aspitia. He added that a final efficacy analysis will be presented in 5 years.

Moreno-Aspitia A, Holmes EM, Jackisch C, et al. Updated results from the phase III ALTTO trial (BIG 2-06; NCCTG (Alliance) N063D) comparing one year of anti-HER2 therapy with lapatinib alone (L), trastuzumab alone (T), their sequence (T→L) or their combination (L+T) in the adjuvant treatment of HER2-positive early breast cancer [ASCO abstract 502]. *J Clin Oncol*. 2017;35(15)(suppl).

Commentary: Lapatinib added to or given instead of adjuvant trastuzumab has been an overall disappointment, with toxicity limiting exposure and little evidence of benefit despite early indications of improved responses in the neoadjuvant setting. Reasons for these results are likely multifactorial and include toxicity management and the inability to identify a population of patients who are more likely to benefit from the addition of lapatinib. Indeed, the more than 8000 patients enrolled on ALTTO had a better outcome than predicted with chemotherapy and trastuzumab alone, which is quite encouraging for our patients with HER2-positive disease.

The strategy of adding oral tyrosine kinase inhibitors (TKIs) to trastuzumab and chemotherapy clearly was not successful. However, extending HER2-targeted therapy with a potent HER2-targeted TKI has met with significant success. In the ExteNET trial (Study Evaluating The Effects Of Neratinib After Adjuvant Trastuzumab In Women With Early Stage Breast Cancer), continuing HER2-targeted therapy with neratinib (Nerlynx, Puma) after the completion of 1 year of adjuvant trastuzumab significantly improved DFS, particularly for patients with hormone receptor–positive, HER2-positive disease. Although neratinib is associated

with a significant risk for grade 3 or higher diarrhea, this can be controlled with prophylactic antidiarrheal therapy. The encouraging results from ExteNET let to approval of neratinib by the FDA as extended adjuvant therapy for HER2-positive early-stage breast cancer in July of 2017.

Adjuvant Paclitaxel/Trastuzumab Linked to Excellent Outcomes in Small HER2-Positive Breast Cancers

The use of adjuvant paclitaxel/trastuzumab is linked to excellent outcomes in patients with small, node-negative, HER2-positive breast cancer, according to updated results from the phase 2 APT trial (Adjuvant Paclitaxel and Trastuzumab for Node-Negative HER2-Positive Breast Cancer). This trial was conducted because women with small tumors are often excluded from trials.

Dr Sara M. Tolaney of the Dana-Farber Cancer Institute presented the results of the trial in a poster. The single-arm study enrolled 406 patients with node-negative, HER2-positive breast cancer less than 3 cm in size. All patients received weekly paclitaxel and trastuzumab for 12 weeks, followed by trastuzumab for 9 months.

After a median follow-up of 6.5 years, the 7-year rate of DFS was 93.3% overall (95% CI, 90.4%-96.2%), 94.6% for hormone receptor–positive patients (95% CI, 91.8%-97.5%), and 90.7% for hormone receptor–negative patients (95% CI, 84.6%-97.2%). A total of 4 distant recurrences occurred. Also at 7 years, the rate was 97.5% for recurrence-free interval, 98.6% for breast cancer–specific survival, and 95.0% for OS.

The investigators recommended that paclitaxel/trastuzumab be considered a standard treatment in patients with stage I HER2-positive breast cancer. Work is ongoing to further differentiate between the various subtypes of HER2-positive tumors.

Tolaney SM, Barry WT, Guo H, et al. Seven-year (yr) follow-up of adjuvant paclitaxel (T) and trastuzumab (H) (APT trial) for node-negative, HER2-positive breast cancer (BC) [ASCO abstract 511]. *J Clin Oncol*. 2017;35(15)(suppl).

Commentary: Long-term follow-up of the APT trial has established this therapy as a new standard of care for small, HER2-positive, early-stage cancers. With just 4 distant recurrences in 406 patients and a 7-year breast cancer–specific survival of 98.6%, this therapy is clearly highly effective. In addition, toxicity was quite modest from the 12 weeks of paclitaxel with 1 year of trastuzumab. For patients who are prescribed trastuzumab-based therapy for stage I HER2-positive cancers, the APT regimen is clearly the regimen of choice, and the addition of pertuzumab is not recommended. At our institution, patients routinely receive scalp cooling to prevent hair loss from this regimen with almost universal success, limiting the impact of adjuvant treatment on their day-to-day lives and shortening the time to recovery.

The recently completely accrued ATEMPT trial (T-DM1 vs Paclitaxel/Trastuzumab for Breast Cancer) evaluated trastuzumab emtansine (Kadcyla, Genentech) as an alternative to the APT regimen for node-negative, HER2-positive breast cancers, randomly assigning patients 3:1 to the experimental arm vs APT. It will be quite interesting to see whether the antibody-drug conjugate given for 1 year is more or less tolerable or can impact efficacy relative to the APT regimen, given the impressive results presented at ASCO.

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