Highlights in Breast Cancer From the 2015 American Society of Clinical Oncology Annual Meeting

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Commentary by Edith A. Perez, MD

Response Rates High for T-DM1 in HER2-Positive/HR-Positive Early Breast Cancer

Women with early breast cancer that is positive for both human epidermal growth factor receptor 2 (HER2) and hormone receptor (HR) have a high response rate to neoadjuvant trastuzumab emtansine (T-DM1; Kadcyla, Genentech)—greater than 40%—even in the absence of endocrine therapy and chemotherapy, according to an interim analysis of the WSG-ADAPT trial.

The analysis also found that adding endocrine therapy to T-DM1 modestly increased response rates in these patients, but only if they were premenopausal. Results were presented by Dr Nadia Harbeck of the University of Munich in Germany.

For the study, women with early breast cancer that was positive for HER2 and HR (either estrogen receptor or progesterone receptor) were randomly assigned to one of 3 neoadjuvant treatment groups for 12 weeks: T-DM1 alone, T-DM1 plus endocrine therapy, or trastuzumab (Herceptin, Genentech) plus endocrine therapy. Endocrine therapy consisted of tamoxifen in premenopausal women and an aromatase inhibitor in postmenopausal women. Patients were scheduled to receive 12 weeks of paclitaxel and 1 year of trastuzumab after surgery. The median age of the patients was 49 years, and 55% of the patients were premenopausal.

A preplanned interim analysis of data on 130 women found that the 3 regimens were safe, with more than 95% of the patients in each group receiving the full treatment. A total of 16 serious adverse events occurred in 13 patients, and 14 of these events led to unplanned hospitalization. All patients recovered completely.

Pathologic complete responses (pCRs) were significantly higher with T-DM1 alone and T-DM1 plus endocrine therapy (40.5% and 45.8%, respectively) than with trastuzumab plus endocrine therapy (6.7%). The number of pCRs was significantly higher among postmenopausal patients than premenopausal patients in the T-DM1–alone group but not in the T-DM1 plus endocrine therapy group. The level of Ki-67 did not aid in predicting pCR, but a low level was associated with early tumor response.

Dr Harbeck emphasized that full data from the WSG-ADAPT study, which includes 380 patients, are required to substantiate these interim findings. She added that treatment with T-DM1 alone warrants further investigation.

Harbeck N, Gluz O, Christgen M, et al. Efficacy of 12-weeks of neoadjuvant TDM1 with or without endocrine therapy in HER2-positive hormone-receptor-positive early breast cancer: WSG-ADAPT HER2+/HR+ phase II trial [ASCO abstract 506]. *J Clin Oncol*. 2015;33(suppl).

Commentary: These early data from a neoadjuvant study corroborate the important role of anti-HER2 therapy in combination with chemotherapy to optimize patient outcome. Moreover, they provide some early evidence that it may be feasible to add an antiestrogenic compound to T-DM1, which consists of trastuzumab linked to a chemotherapy agent.

T-DM1 Noninferior to Trastuzumab/Taxane in HER2-Positive Breast Cancer

Treatment with T-DM1, either alone or in combination with pertuzumab (Perjeta, Genentech), produces noninferior progression-free survival (PFS) compared with the standard first-line treatment for HER2-positive metastatic breast cancer (trastuzumab and a taxane), according to primary results from the phase 3 MARIANNE study. The addition of pertuzumab to T-DM1 did not improve PFS.

Although T-DM1 did not produce superior PFS, it was better tolerated than standard treatment, said Dr Paul Ellis of Guy's Hospital and Sarah Cannon Research Center in London, the United Kingdom, who presented the results.

For the study, researchers assigned 1095 women with HER2-positive, locally advanced or metastatic breast cancer to one of 3 groups: trastuzumab plus a taxane (docetaxel or paclitaxel), T-DM1 plus placebo, or T-DM1 plus pertuzumab. Randomization to placebo or pertuzumab was blinded.

The median age of the patients was 52 to 55 years, 21% were premenopausal, and 66% to 71% had visceral metastases. Between 44% and 45% of the patients had received no prior neoadjuvant or adjuvant treatment, and approximately one-third had received adjuvant HER2-directed treatment.

After a median follow-up of 35 months, PFS was 13.7 months in the trastuzumab/taxane group, 14.1 months in the T-DM1/placebo group, and 15.2 months in the T-DM1/pertuzumab group. Both of the T-DM1–containing arms demonstrated noninferior PFS compared with the standard treatment arm, but did not

demonstrate superior PFS. The addition of pertuzumab to T-DM1 did not improve PFS.

Dr Ellis said that median overall survival (OS) had not been reached, and that patients were still being followed for survival status. Although the objective response rate was lower in the T-DM1/placebo arm (59.7%) than in the trastuzumab/taxane or T-DM1/pertuzumab groups (67.9% and 64.2%, respectively), the duration of response was longer in both T-DM1–containing groups (approximately 21%) than in the trastuzumab/taxane group (12.5%).

A 5-point decrease in Health-Related Quality of Life score took longer to occur in the T-DM1/placebo and T-DM1/pertuzumab groups (7.7 and 9.0 months, respectively) than in the trastuzumab/taxane group (3.6 months). There were also fewer high-grade adverse events, or adverse events leading to discontinuation of any treatment component, in the T-DM1–containing groups compared with the trastuzumab/taxane group.

The grade 3 or 4 adverse events that were more common in the trastuzumab/taxane group were neutropenia, febrile neutropenia, and diarrhea, whereas those that were more common in the T-DM1-containing groups were hypertension, anemia, an increase in transaminases, and thrombocytopenia. The rate of alopecia was much lower in the T-DM1–containing arms (6.6% to 9.0%) than in the trastuzumab/taxane arm (59.8%).

Dr Ellis concluded that T-DM1 is "an alternative treatment option" to trastuzumab/taxane in previously treated patients with HER2-positive metastatic breast cancer.

Ellis PA, Barrios CH, Eiermann W, et al. Phase III, randomized study of trastuzumab emtansine (T-DM1) ± pertuzumab (P) vs trastuzumab + taxane (HT) for first-line treatment of HER2-positive MBC: primary results from the MARIANNE study [ASCO abstract 507]. *J Clin Oncol*. 2015;33(suppl).

Commentary: I am the senior investigator on this presentation. This is a well-conducted global trial with 2 main summary results. First, T-DM1 is noninferior to trastuzumab plus taxane but with improved side effects. Second, pertuzumab plus T-DM1 is not superior to T-DM1 alone. These results are highly impactful in clinical practice for patients with advanced HER2-positive breast cancer, but also have implications for research in the adjuvant setting.

Neratinib Reduces Recurrence in Patients With HER2-Positive Early Breast Cancer

Recurrence is common after treatment of HER2-positive early breast cancer with trastuzumab and chemotherapy. Now, a primary analysis of a phase 3 study finds that the use of neratinib, an experimental oral tyrosine kinase inhibitor of HER1, 2, and 4, improves invasive disease-free survival (DFS) in these women at 2 years.

Dr Arlene Chan of the Breast Cancer Research Centre of Western Australia in Perth, Australia, presented the results of the trial, called ExteNET. The study involved randomly assigning 2840 women with local, HER2-positive breast cancer and prior treatment with adjuvant trastuzumab and chemotherapy to 1 year of either neratinib 240 mg daily or placebo.

Dr Chan noted that the study underwent several amendments because of changes in sponsorship. For example, the original protocol required the women to have stage 1, 2, or 3 breast cancer that had not been treated with trastuzumab for more than 2 years; that was later amended to women with stage 2 or 3 breast cancer that had not been treated with trastuzumab for more than 1 year. The length of follow-up, which was originally 5 years, was truncated to 2 years and then restored to 5 years.

Dr Chan said that there were "no major imbalances" between the 2 groups at baseline. After a follow-up of 2 years, the rate of invasive DFS—the primary endpoint of the study—was significantly better in the neratinib group (93.9%) than the placebo group (91.6%). This advantage of neratinib held across all subsets, and was unaffected by age, nodal status, or trastuzumab schedule. There also were fewer invasive disease-free events in the neratinib group, such as local or regional invasive recurrence and contralateral breast cancer. Most importantly, said Dr Chan, there was less distant recurrence in the neratinib group than in the placebo group.

Regarding the secondary endpoints, DFS was superior with neratinib treatment vs placebo, including ductal carcinoma in situ (93.9% vs 91.0%). In the subset of patients in which the tumors were found to be HER2-positive by central testing (data were presented based on approximately 60% of patients enrolled in the trial), there appeared to be increased benefit from adding neratinib. Women whose tumors were HR-positive received even greater benefit from neratinib: the rate of invasive DFS was 95.4% with neratinib and 91.2% with placebo for HR-positive women. However, a statistically significant benefit in those with HR-negative disease was not observed.

As expected, the most common grade 3 or higher adverse event with neratinib was diarrhea (39.9%). More than 90% of patients reported diarrhea. The median duration of diarrhea was 5 days, and most cases occurred within 30 days of treatment.

Dr Chan cautioned that this 2-year follow-up was too brief to assess overall survival, but concluded that 12 months of neratinib had a significant benefit in invasive DFS at 2 years. The finding that neratinib was especially

beneficial in HR-positive disease requires further study. She recommended the prophylactic use of loperamide to make neratinib therapy "far more tolerable" for patients.

Chan A, Delaloge S, Holmes FA, et al. Neratinib after adjuvant chemotherapy and trastuzumab in HER2-positive early breast cancer: primary analysis at 2 years of a phase 3, randomized, placebo-controlled trial (ExteNET) [ASCO abstract 508]. *J Clin Oncol*. 2015;33(suppl).

Commentary: The results of this study are preliminary based on the short follow-up and other factors. The reported benefit in patients whose disease is HR-positive, but not in those whose disease is HR-negative, is not intuitive. In other trials of agents against HER2-positive disease, the majority of events in the first 5 years occurred in patients with HR-negative disease. In terms of tolerability, the rate of adverse events was high; it will be important to learn details about potential ways to minimize these effects.

Palbociclib Improves PFS in HR-Positive Advanced Breast Cancer

A combination of palbociclib (Ibrance, Pfizer) and fulvestrant improved PFS in patients with HR-positive advanced breast cancer that had progressed on prior endocrine therapy, according to results of the PALOMA-3 study. Resistance to endocrine therapy is a major clinical problem for patients with HR-positive breast cancer, affecting approximately one-quarter of patients. Palbociclib is an orally active selective inhibitor of the cyclin-dependent kinases CDK4/6, which contribute to endocrine therapy resistance.

Dr Nicholas Turner of Royal Marsden Hospital in London, the United Kingdom, presented the results of the phase 3, double-blinded study. A total of 521 patients with HR-positive, HER2-negative advanced breast cancer that had progressed on prior endocrine therapy were randomly assigned to receive fulvestrant plus either palbociclib (125 mg per day; 3 weeks on and 1 week off) or placebo. Patients in the 2 groups were comparable in terms of median age (56 to 57 years), premenopausal status (21%), and number of disease sites (39% had 3 or more).

After 1 year of follow-up, PFS was significantly higher with palbociclib (9.2 months) than with placebo (3.8 months). A patient subgroup analysis found that PFS was similar in premenopausal patients, who received goserelin, and postmenopausal patients. The clinical benefit rate was significantly better with palbociclib (34%) than with placebo (19%). OS data were immature, with only 28 deaths.

The overall incidence of serious adverse events was similar between the palbociclib group (9.6%) and the placebo group (14.0%), but interruptions in treatment caused by adverse events were more common with palbociclib (54%) than with placebo (4%). Neutropenia was the adverse event that led to the most dose reductions and interruptions. Patients in the palbociclib group were more likely to experience hematologic side effects such as neutropenia, leukopenia, anemia, and thrombocytopenia than those in the placebo group. Adverse events and toxicity did not cause any deaths.

Dr Turner concluded that fulvestrant plus palbociclib is "an effective treatment option" for women with HR-positive, HER2-negative advanced breast cancer whose disease had progressed on prior endocrine therapy.

Turner NC, Ro J, Andre F, et al. PALOMA3: a double-blind, phase III trial of fulvestrant with or without palbociclib in pre- and post-menopausal women with hormone receptor-positive, HER2-negative metastatic breast cancer that progressed on prior endocrine therapy [ASCO abstract LBA502]. *J Clin Oncol*. 2015;33(suppl).

Commentary: This is an important study regarding the evolution of combination strategies for patients with HR-positive breast cancer. Assessment of the cost-to-benefit ratio of adding palbociclib should be performed. Awaiting survival data will be very important, but it is good to learn that we have an agent that helps improve PFS in the second-line setting.

Etirinotecan Pegol Improves OS in Subgroups of Patients With Breast Cancer

Etirinotecan pegol (EP) improves overall survival in certain subgroups of patients with advanced breast cancer, according to the results of the phase 3 BEACON study, presented by Dr Edith Perez of the Mayo Clinic in Jacksonville, Florida.

The study was based on 852 patients with advanced breast cancer who had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and had previously been treated with an anthracycline, a taxane, and capecitabine. Patients were randomly assigned to receive either physician's choice of single-agent chemotherapy (eribulin, vinorelbine, gemcitabine, taxane, or ixabepilone [Ixempra, Bristol-Myers Squibb]) or EP, a topoisomerase 1 inhibitor.

Patients treated with EP did not have a significant improvement in median OS compared with those treated with physician's choice (12.4 vs 10.3 months, respectively; P=.08). In the prespecified subgroup of patients with a history of brain metastases (67 patients), patients treated with EP had a significant improvement in median OS compared with physician's choice (10 vs 4.8 months, respectively; P<.01). The percentage of patients who had brain metasta-

ses and were still alive at 12 months was also higher with EP treatment (44.4% vs 19.4%, respectively). In a subgroup of patients with liver metastases (456 patients), patients treated with EP showed a significant improvement in OS compared with physician's choice (10.9 vs 8.3 months, respectively; *P*<.002). Quality of life was better in patients receiving EP than in those receiving physician's choice.

Researchers also examined circulating tumor cells to identify biomarker-defined subgroups, and found a decrease in the number of topoisomerase 1–positive cells after treatment with EP. OS was higher in patients who had lower levels of topoisomerase 1 after EP treatment compared with those whose levels remained high (14.9 vs 10.7 months, respectively; *P*=.007). Further analysis of specific biomarkers is ongoing.

The most common grade 3 or higher adverse events with EP included diarrhea, neutropenia, anemia, and fatigue. The most common adverse events of any grade with EP included diarrhea, nausea, vomiting, decreased appetite, and abdominal pain. Some adverse events were more common in patients treated with physician's choice than with EP, including neutropenia, infections, asthenia, severe neuropathy, and alopecia.

Dr Perez noted that, despite the lack of significant change in patients overall, these "provocative and potentially very important survival results in predefined subgroups of patients deserve further study, specifically patients with brain metastases or liver metastases."

Perez EA, Awada A, O'Shaughnessy J, et al. Phase III trial of etirinotecan pegol (EP) versus treatment of physician's choice (TPC) in patients (pts) with advanced breast cancer (aBC) whose disease has progressed following anthracycline (A), taxane (T) and capecitabine (C): the BEACON study [ASCO abstract 1001]. *J Clin Oncol*. 2015;33(suppl).

Commentary: As the presenter and coprincipal investigator of this trial, I think this is a well-conducted global trial that provides important and relevant information. Several factors for consideration include that the comparator arm was chemotherapy of physician's choice; that is, what the physicians felt was "the best" they could offer their patients. Etirinotecan pegol led to a 2.1-month improvement in survival that lasted up to 15 months from study entry, but not thereafter. There was a nonproportional hazard for recurrence, which was different than the proportional hazard that was part of the study's statistical design. The benefit observed in patients with liver metastases and also those with history of brain metastases is notable. Moreover, the side effect profile and quality of life analyses favored etirinotecan pegol. Based on the data, I believe this agent could be considered for practice if it were available. More studies are warranted.

Enzalutamide Shows Clinical Benefit in Patients With Androgen Receptor–Positive Breast Cancer

Enzalutamide (Xtandi, Astellas/Medivation), an androgen receptor inhibitor that is US Food and Drug Administration (FDA)–approved for prostate cancer, also provides a clinical benefit to patients with triple-negative breast cancer (TNBC) who are androgen receptor–positive, according to a phase 2 study presented by Dr Tiffany A. Traina of Memorial Sloan Kettering Cancer Center in New York, New York. Dr Traina noted that "the role of the androgen receptor in breast cancer is becoming increasingly apparent."

This study included 118 patients in the intent-to-treat population who were screened for androgen receptor positivity using immunohistochemistry with a cutoff of 10% or greater. Of these patients, 75 were positive for the androgen receptor and had a post-baseline assessment, making them part of the evaluable population. All 118 patients were treated with enzalutamide (160 mg per day orally), and more than half of the patients received enzalutamide as first- or second-line therapy. The primary endpoint was clinical benefit rate (CBR; defined as complete response, partial response, or stable disease) at 16 or 24 weeks.

The CBR of the evaluable patients was 35% at 16 weeks and 29% at 24 weeks, a statistically significant finding. The researchers identified 2 patients with complete responses and 5 with partial responses. The median PFS was 14.7 weeks.

The researchers also used a diagnostic assay (called PREDICT AR) to further identify patients with an androgen-driven gene signature. The CBR was higher in the PREDICT AR–positive group than the negative group at 16 weeks (39% vs 11%, respectively) and 24 weeks (36% vs 6%, respectively). The PREDICT AR–positive patients also had a higher rate of complete and partial responses (9% vs 3%, respectively) and a higher median PFS (16.1 vs 8.1 weeks, respectively). For patients with 0 or 1 prior therapies, this difference was even greater (40.4 vs 8.9 weeks, respectively). The median OS assessment is still ongoing for these patients.

The safety data are similar to those seen previously with enzalutamide in prostate cancer. Common adverse events included fatigue, nausea, decreased appetite, diarrhea, and hot flashes. The only grade 3 or higher adverse event was fatigue.

Dr Traina noted, "we find results of this phase 2 study to be compelling and warrant further investigation and development of enzalutamide for the treatment of patients with metastatic TNBC enriched by that biomarker."

Traina TA, Miller K, Yardley DA, et al. Results from a phase 2 study of enzalutamide (ENZA), an androgen receptor (AR) inhibitor, in advanced AR+ triple-negative breast cancer (TNBC) [ASCO abstract 1003]. *J Clin Oncol*. 2015;33(suppl).

Commentary: This study demonstrated modest activity of enzalutamide in TNBC, such that additional studies are warranted. The fact that the main endpoint was clinical benefit rate makes it challenging to interpret how beneficial this drug will be, but will impact the decision of what endpoint scenarios are projected for response—PFS or OS—as primary endpoints for further comparative studies.

Homologous Recombination Deficiency Predicts Response to Adjuvant Chemotherapy in TNBC

The presence of homologous recombination deficiency (HRD) predicted pCR to an adjuvant chemotherapy regimen (paclitaxel and liposomal doxorubicin [Doxil, Janssen]) in patients with TNBC irrespective of the addition of carboplatin, according to the GeparSixto trial presented by Dr Gunter Von Minckwitz of the German Breast Group in Neu-Isenburg, Germany.

Dr Von Minckwitz noted that the goal of this study was to define patients who "may respond better to carboplatin."

This study included 193 patients with TNBC who received paclitaxel and liposomal doxorubicin with or without carboplatin. HRD, which measures DNA repair capacity, was assessed in all 193 patients. A sample was considered to be positive for HRD if the HRD score was high (≥42 out of 100) or the tumor contained a *BRCA* mutation. HRD was found in 136 samples (70.5%), and 82 (60.3%) of these samples had a high HRD score without a *BRCA* mutation.

The CR rate was higher in HRD tumors than in non-HRD tumors (55.9% vs 29.8%, respectively; *P*=.001). In HRD tumors, the regimen with carboplatin had a higher CR rate than the regimen without carboplatin (64.9% vs 45.2%, respectively; *P*=.025). In non-HRD tumors, the difference was not significant (40.7% vs 20.0%, respectively; *P*=.146). In patients with no *BRCA* mutation, a higher CR rate was found in those with a high HRD score vs a low HRD score (49.4% vs 30.9%; *P*=.050), irrespective carboplatin addition.

Using one assessment of CR, carboplatin addition increased the CR rate in patients with *BCRA*-mutated tumors (69.7% with carboplatin vs 38.1% without carboplatin; *P*=.022). Patients with a high HRD score and no *BRCA* mutation also had a better CR rate with the addition of carboplatin (63.2% vs 31.7%, respectively; *P*=.005). Non-HRD tumors showed no significant difference in CR with or without carboplatin (29.6% vs 20.0%, respectively; *P*=.399). However, using a different definition of pCR, no significant interactions were found.

Dr Von Minckwitz concluded that HRD is an independent predictor of high pCR rates in TNBC after chemotherapy with or without carboplatin. He noted that HRD tests may be used to identify which patients are likely to respond to DNA-damaging agents, but also cautioned that "these data have to be confirmed by other studies… and set into context with survival data."

Von Minckwitz G, Timms K, Untch M, et al. Prediction of pathological complete response (pCR) by homologous recombination deficiency (HRD) after carboplatin-containing neoadjuvant chemotherapy in patients with TNBC: results from GeparSixto [ASCO abstract 1004]. *J Clin Oncol.* 2015;33(suppl).

Commentary: A role for HRD testing in therapeutic decision-making has not been established

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