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Recent Advances in the Treatment of Breast Cancer: Highlights From the 2010 San Antonio Breast Cancer Symposium

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Abstract

The annual San Antonio Breast Cancer Symposium (SABCS) remains one of the most important meetings in the field of breast cancer. SABCS is a forum to present relevant information, combining discussions and presentations in the setting of basic research, translational research, and clinical cancer research. Many of these studies impact patient management and guide the development of new research strategies. The 2010 SABCS was very well attended by investigators, clinicians, and allied health professionals from multiple countries. Presentations at the meeting addressed specific topics, including prevention, management of patients in the early and advanced stage settings, and utilization of molecular markers for research strategies. There were many areas that disclosed important information for clinicians and patients. The abstracts included in this supplement concentrate on advancements in the management of breast cancer patients with both early-stage and advanced-stage disease.

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Target Audience

This activity has been designed to meet the educational needs of oncologists and other healthcare professionals who treat patients with breast cancer.

Statement of Need/Program Overview

The treatment of breast cancer continues to rapidly evolve, and clinicians must be able to integrate the most recent therapeutic advances into their practice in order to maximize outcomes for their patients. The San Antonio Breast Cancer Symposium (SABCS) is one of the premier outlets for the release of new clinical data regarding breast cancer. Presentations at the 2010 SABCS addressed topics such as management of patients in the early and advanced stage settings, and utilization of molecular markers. Many of these studies will impact patient management and guide the development of new research strategies.

Educational Objectives

After completing this activity, the participant should be better able to:

- Analyze the benefits and limitations of current treatment strategies for breast cancer
- Interpret recent clinical data in the management of breast cancer
- Define strategies for integrating new information into clinical practice
- Assess clinical data on emerging treatment strategies in patients with breast cancer
- Identify ongoing clinical trials that are expected to impact clinical practice
- Outline strategies for the integration of new agents into current clinical practice

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Management of Early Breast Cancer

Harold J. Burstein, MD, PhD

Many abstracts of note were presented at the 2010 San Antonio Breast Cancer Symposium (SABCS) regarding early-stage breast cancer. These studies largely dealt with advancements in both basic and clinical breast cancer research. Some of the most clinically relevant of these abstracts are discussed here.

Surgical Management

A sentinel node biopsy allows a very detailed analysis of the axillary nodes, and thus permits a greater chance of detection of both micrometastatic and macrometastatic nodal breast cancer. Further, the goal of sentinel node surgery is to achieve the same outcomes as gained with axillary node dissection, but with fewer adverse events.

In one study examining sentinel lymph node dissection, some of the most important findings concerned the prognostic significance of micrometastatic disease. An analysis of prospective outcomes from patients in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32, presented by Julian and colleagues, assessed the value of a complete axillary dissection in patients with operable invasive breast cancer.[1] The NSABP B-32 study was a randomized, phase III trial in which breast cancer patients with clinically negative axillary nodes underwent sentinel node resection that was either always followed by axillary dissection or followed by axillary dissection only when the sentinel node was found to be positive by hematoxylin and eosin staining.[2] Patients were stratified at randomization according to age, clinical tumor size, and surgical plan. Systemic therapy, regional nodal irradiation for node-positive lumpectomy patients, and chest wall/regional node irradiation for node-positive mastectomy patients were permitted at the discretion of the physician. Between 1999 and 2004, 5,611 patients were enrolled into the NSABP B-32 trial; this analysis included women (N=1,389) with complete follow-up data who were found to have a positive sentinel node.

Macrometastases, defined as greater than 2 mm in size, were identified in 422 patients; micrometastases, defined as between 0.2 and 2.0 mm in size, were identified in 312 patients; and 626 patients had unknown status. Almost all sentinel node-positive patients (97%) received systemic adjuvant treatment. The median time that patients were included in the study was 94 months.

In a univariate analysis, several factors were determined to be predictive of overall survival (OS) and disease-free survival (DFS), including age, receptor status, clinical tumor size, histologic grade, number of positive sentinel nodes, sentinel node metastasis size, number of positive nodes, lymphovascular invasion, and systemic therapy. A number of these factors remained significant in multivariate analysis, including histologic grade (intermediate vs good: hazard ratio [HR], 0.83; 95% confidence interval [CI], 0.44–1.439; $P<.0001$; poor vs good: HR, 2.30; 95% CI, 1.32–4.034; $P<.0001$), sentinel node metastasis (macrometastasis vs micrometastasis: HR, 2.44; 95% CI, 1.51–3.95; $P=.0003$), clinical tumor size (HR, 1.21; 95% CI, 1.05–1.39; $P=.01$), number of positive axillary nodes (HR, 1.09; 95% CI, 1.06–1.13; $P<.0001$), age (HR, 1.04; 95% CI, 1.02–1.06; $P<.0001$), and use of adjuvant therapy (HR, 0.22; 95% CI, 0.11–0.42; $P<.0001$). These factors were similarly predictive for DFS.

One of the more important findings from these data is that the most significant factor associated with poor patient outcomes (OS and DFS) was the presence of macrometastases versus micrometastases, and that women with micrometastases present in their sentinel lymph node have the same prognosis as women with node-negative breast cancer. Thus, these results suggest that physicians should consider patients with evidence of micrometastatic disease in even a single lymph node as having a prognosis more similar to patients with node-negative disease, and that these patients may not benefit from axillary dissection. Interestingly, those patients with either type of sentinel node metastases who received systemic therapy experienced a 78% reduction in mortality and a 76% improvement in DFS.

Adjuvant Chemotherapy

Perhaps one of the most eagerly anticipated studies at the 2010 SABCS was the AZURE (Adjuvant Zoledronic Acid to Reduce Recurrence) study, a randomized, open-label, multicenter, international, parallel-group, phase III trial presented by Coleman and colleagues.[3] This study evaluated whether the addition of zoledronic acid to standard adjuvant therapy had any effect on breast cancer recurrence in early-stage breast cancer, and was based on promising results from the ABCSG-12 (Austrian Breast and Colorectal Cancer Study Group trial-12) study, which demonstrated a benefit in DFS with zoledronic acid in premenopausal women with hormone receptor–positive early-stage breast cancer who were treated with goserelin and either tamoxifen or anastrozole.[4] In the current study, patients (N=3,359) with early-stage breast cancer were randomized to standard adjuvant therapy (either endocrine therapy, chemotherapy, or both) given either with

or without 4 mg zoledronic acid (every 3–4 weeks during months 1–6, every 3 months during months 6–30, and every 6 months during months 30–60).

Overall, there was no significant difference in the DFS among patients who did or did not receive zoledronic acid (HR, 0.98, 95% CI, 0.85–1.13; *P*=.79). Although there was a trend toward a prolonged OS among zoledronic acid–treated patients, it did not reach statistical significance (HR, 0.85, 95% CI, 0.72–1.01; *P*=.07). However, a subgroup analysis found a significant improvement in DFS among zoledronic acid–treated patients who were more than 5 years beyond menopause (odds ratio 0.76, 95% CI, 0.60–0.98), and in OS among postmenopausal women (HR, 0.71, 95% CI, 0.54–0.94; *P*=.017).

It is difficult to reconcile these findings from the AZURE study with those previously reported from the ABCSG-12 trial. This larger study demonstrated no substantial benefit, and this outcome is likely to ultimately be the correct interpretation. There is some interest in trying to evaluate if certain patient subsets defined by menopausal status would benefit from the addition of zoledronic acid. Overall, this study is an important negative result, showing that the bisphosphonate zoledronic acid does not lower the risk of cancer recurrence when included with adjuvant therapy.

Current guidelines recommend that adjuvant systemic therapy should be considered in all patients with early-stage breast cancer who are younger than 70 years.[5] Depending on the exact regimen chosen, either 4 or 6 cycles of chemotherapy are used in the adjuvant setting. Shulman and colleagues presented the first results of the Cancer and Leukemia Group B (CALGB) 40101 study, which used a phase III, 2 × 2 factorial design to assess if 6 cycles or 4 cycles of a chemotherapy regimen were superior in patients with low-risk primary breast cancer.[6] Patients (N=3,173) with operable breast cancer and 0–3 positive lymph nodes were enrolled. They were stratified by hormone receptor, human epidermal growth factor receptor type 2 (HER2) status, and menopausal status, and then randomized to treatment with either doxorubicin plus cyclophosphamide (4 vs 6 cycles) or paclitaxel (4 vs 6 cycles) adjuvant chemotherapy. At the time of study initiation, doxorubicin (60 mg/m^2) plus cyclophosphamide (600 mg/m^2) was administered every 3 weeks for 4 or 6 cycles, and paclitaxel (80 mg/m^2) was administered weekly for 12 or 18 weeks. The treatment schedule was subsequently changed to every 2 weeks for both doxorubicin plus cyclophosphamide and paclitaxel (175 mg/m^2). Enrollment of patients to the 6-cycle regimens was permanently closed in 2008 due to slow accrual. Although data comparing doxorubicin plus cyclophosphamide versus paclitaxel were not available at the time of this presentation, results comparing the superiority of 6 versus 4 chemotherapy cycles were presented. The vast majority (94%) of patients randomized to 6 cycles versus 4 cycles of chemotherapy had node-negative disease.

After a median follow-up of 4.6 years (range: 2.5–8 years), the 4-year rate of relapse-free survival was very similar between the 6-cycle and 4-cycle treatment groups (91.6% vs 91.8%, HR, 1.10, 95% CI, 0.87–1.39; *P*=.42). Similarly, there was no significant difference in the rate of 4-year OS between the 2 treatment groups (95.3% vs 96.4%, HR, 1.31, 95% CI, 0.95–1.82; *P*=.097). No association was found between the number of treatment cycles and the type of chemotherapy, hormone receptor status, or HER2 status. Based on the number of relapse-free survival events included in this analysis, the Bayesian predictive probability of superiority of 6 versus 4 chemotherapy cycles was determined to be 0.001. Thus, there was no evidence supporting the use of 6 cycles versus 4 cycles of chemotherapy to improve patient outcomes in women with early-stage breast cancer with 0–3 positive lymph nodes.

In patients with metastatic breast cancer, capecitabine has been found to improve survival when added to docetaxel.[7] Further, capecitabine was shown to be beneficial when added to an anthracycline/taxane-containing neoadjuvant regimen.[8,9] Thus, a potential benefit of capecitabine in adjuvant therapy for women with early-stage breast cancer has also been speculated. Two studies evaluated the role of capecitabine in this setting; the overall results from both suggested that adding capecitabine to adjuvant therapy for high-risk disease may be beneficial, but neither of the studies were found to be practice-changing.

A final analysis of the FinXX study, a randomized, open-label, controlled, multicenter, phase III clinical trial, was reported by Joensuu and colleagues.[10] Patients (N=1,500) with high-risk early breast cancer were randomized to receive 6 cycles of either a non–capecitabine-containing regimen (3-week cycles of T-CEF: 80 mg/m^2 docetaxel on day 1 of cycles 1–3, 600 mg/m^2 cyclophosphamide on day 1, 75 mg/m^2 epirubicin on day 1, and 600 mg/m^2 5-fluorouracil on day 1 for cycles 4–6) or a capecitabine-containing regimen (3-week cycles of TX-CEX: 60 mg/m^2 docetaxel on day 1, 900 mg/m^2 capecitabine twice daily on days 1–15, 600 mg/m^2 cyclophosphamide on day 1, and 75 mg/m^2 epirubicin on day 1). Patients were stratified by the number of involved lymph nodes, HER2 status, and study site. Once completing chemotherapy, estrogen receptor (ER)-positive patients went on to receive endocrine therapy (anastrozole plus tamoxifen) for 5 years. High-risk disease was defined as the presence of either lymph node positive status or tumor size greater than 20 mm, progesterone receptor (PR)-negative status, and lymph node negative status. Women older than 65 years were excluded from enrollment. This analysis included a 5-year patient follow-up.

Interim 3-year analysis results of this study demonstrated a 34% reduction in the risk of breast cancer recurrence with the addition of capecitabine.[8] When comparing the T-CEF versus TX-CEX arms, no significant differences were observed in either the 5-year relapse-free survival rate (84.1% vs 86.6%; HR, 0.79; 95% CI, 0.60–1.04; *P*=.087) or the 5-year OS rate (89.7% vs 92.6%; HR, 0.73; 95% CI, 0.52–1.04; *P*=.08). However, a small but statistically significant improvement was observed with the capecitabine-containing regimen in terms of breast cancer–specific survival (91.0% vs 94.4%; HR, 0.64; 95% CI, 0.44–0.95; *P*=.027). Additionally, exploratory subgroup analyses also demonstrated a significant increase in the time to recurrence with TX-CEX versus T-CEF specifically in patients with more than 3 lymph nodes involved, and in the relapse-free survival in patients with triple-negative breast cancer (HR, 0.48; *P*=.0177). Fewer patients completed all 6 cycles of chemotherapy in the TX-CEX arm compared with the T-CEF arm (75% vs 96%); discontinuation was most frequently due to toxicity. The most common adverse events reported in significantly more patients in the TX-CEX group included hand-foot syndrome, nail conditions, and stomatitis. The most frequently reported adverse events that occurred significantly more in the T-CEF group included neutropenia, amenorrhea, infection with neutropenia, febrile neutropenia, and myalgia.

A second study evaluating capecitabine in adjuvant breast cancer therapy was the US Oncology 01062 study, presented by O'Shaughnessy and colleagues.[11] These data were the first efficacy results from this randomized, multicenter, phase III study. All patients (N=2,611) had high-risk early breast cancer, defined as the presence of either 1 or more positive lymph nodes and T1–3 disease, node-negative disease with tumors greater than 2 cm, or node-negative disease with tumors greater than 1 cm that were hormone receptor–negative. Patients were treated with four 3-week cycles of adjuvant 60 mg/m^2 doxorubicin on day 1 plus 600 mg/m^2 cyclophosphamide on day 1, followed by four 3-week cycles of 100 mg/m^2 docetaxel on day 1 given either alone or with 825 mg/m^2 capecitabine twice daily on days 1–14 (when given with capecitabine, docetaxel was lowered to 75 mg/m^2). Patients with hormone receptor–positive disease further underwent 5 years of tamoxifen on aromatase inhibitor therapy; after 2005, patients with HER2-positive disease were also offered trastuzumab.

After a median follow-up of 5 years, the primary study endpoint of DFS was not met between the capecitabine versus no capecitabine arms (5-year DFS: 89% vs 87%; HR, 0.8; 95% CI, 0.67–1.05; *P*=.125). However, a significant improvement in 5-year OS was apparent with the addition of capecitabine (94% vs 92%; HR, 0.68; 95% CI, 0.51–0.92; *P*=.011). Exploratory analyses also showed a trend in DFS and OS improvements that favored the addition of capecitabine, including in patients with lymph node involvement, hormone receptor–negative patients, Hispanic patients, and in patients with Ki-67 expression at or greater than 10%. The frequency of adverse events was relatively similar between the treatment arms, although patients treated with the capecitabine-containing regimen reported a higher incidence of grade 3 hand-foot syndrome, grade 3/4 stomatitis, and grade 3/4 diarrhea.

Adjuvant Endocrine Therapy

A number of studies evaluated adjuvant endocrine therapy in order to attempt to identify an optimal aromatase inhibitor for early-stage breast cancer. Aromatase inhibitors differ mainly according to their distinct structural characteristics (steroidal vs nonsteroidal) and activity (irreversible vs reversible inhibition, ability to induce androgenic effects).

In postmenopausal women with early-stage breast cancer, anastrozole is currently indicated for first-line adjuvant therapy, whereas exemestane is approved for use only after 2–3 years of initial adjuvant tamoxifen treatment. Goss and colleagues presented the NCIC CTG MA.27 (National Cancer Institute of Canada Clinical Trials Group MA.27) study, a randomized, open-label, phase III trial that compared the safety and efficacy of these 2 aromatase inhibitors as first-line adjuvant therapy.[12] Postmenopausal patients (N=7,576) with hormone receptor–positive early breast cancer were included and stratified by lymph node status, use of adjuvant chemotherapy, trastuzumab use, and celecoxib or aspirin use. Patients were randomized to receive either 25 mg/day exemestane or 1 mg/day anastrozole as adjuvant endocrine therapy, which was continued for 5 years.

The primary study endpoint, event-free survival, was comparable between the exemestane and anastrozole treatment arms (9.2% vs 9.1% events; HR, 1.02; 95% CI, 0.87–1.18; *P*=.85). This similarity was evident both in the overall treatment population as well as when comparing patients in terms of whether they had node-positive versus node-negative disease and whether they had undergone chemotherapy treatment. Similarly, other efficacy outcomes were also found to be comparable between the 2 treatment arms, including OS (5.5% vs 5.9% events; HR, 0.93; 95% CI, 0.77–1.13; *P*=.64), distant DFS (4.1% vs 4.3% events; HR, 0.95; 95% CI, 0.76–1.18; *P*=.46), and disease-specific survival (2.4% vs 2.6% events; HR, 0.93; 95% CI, 0.70–1.24; *P*=.62). Exemestane was associated with a significantly higher frequency of steroidal-related effects (including alterations in alanine aminotransferase, aspartate aminotransferase, and bilirubin levels, as well as acne and masculinization) and slightly higher rates of atrial fibrillation (1.9% vs 1.2%; *P*=.02). Anastrozole

was associated with significantly higher rates of elevated triglycerides (3.3% vs 2.1%; *P*=.002) and elevated cholesterol (17.7% vs 15.3%; *P*=.01), as well as patient-reported new-onset osteoporosis (35% vs 31%; *P*=.001). However, there was no significant difference in the frequency of treatment discontinuation between either aromatase inhibitor treatment. Thus, this trial demonstrated comparable efficacy and safety between these 2 aromatase inhibitors and suggests that exemestane may be a new alternative for first-line adjuvant therapy in postmenopausal women.

One of the more frequent complaints among breast cancer patients regarding aromatase inhibitors is the development of musculoskeletal symptoms, including arthralgias. Henry and colleagues reported on the use of duloxetine,[13] a serotonin and norepinephrine receptor inhibitor that has demonstrated efficacy in the treatment of chronic pain,[14] to treat the aromatase inhibitor–associated musculoskeletal syndrome. This was a single-arm, open-label, phase II clinical trial of postmenopausal patients (N=35) who had received 2 or more weeks of aromatase inhibitor therapy and had developed either new or worsening musculoskeletal pain after initiating treatment. Patients received duloxetine (30 mg/day for 1 week, followed by 60 mg/day for 3 weeks) and had the option of continuing duloxetine at 60 mg/day or increasing the dose to 60 mg twice daily for the next 4 weeks. Only 20 patients completed the 8-week study period and were included in this analysis; 6 patients discontinued treatment early due to duloxetine-related toxicity, and 9 patients had not yet completed the study period before analysis (N=26 evaluable patients). A total of 70% of the 20 patients who had completed the study treatment elected to continue duloxetine therapy. Over half (61.5%) of the 26 evaluable patients experienced at least a 30% decrease in average pain. Both average pain severity and maximum pain severity were significantly reduced from baseline to 8 weeks (*P*<.0001 for both). The mean percent reduction in average pain severity between baseline and 8 weeks was 56.1% (95% CI, 37.9–74.2), and the mean percent reduction in maximum pain severity was 55.7% (95% CI, 37.3–74.1). No grade 3/4 toxicities were reported.

Several recent reports have suggested that the benefits of tamoxifen therapy are dependent upon the pharmacogenomic profile of the patient. In particular, the polymorphisms in the *CYP2D6* drug metabolizing gene have been associated with clinical outcomes in tamoxifen-treated patients with early-stage breast cancer, showing that patients with a poor-metabolizing phenotype have worse outcomes, whereas patients with an extensive-metabolizing phenotype have better outcomes.[15] Additionally, the *CYP2D6* phenotype has been associated with the development of tamoxifen-related toxicities, with poor metabolizing phenotype patients having a lower risk of hot flashes.[16,17] However, much of the research addressing this issue has involved studies with relatively small patient populations, incomplete genotype data, and incomplete clinical outcome data. Thus, 2 presentations at the 2010 SABCS investigated the role of *CYP2D6* metabolism and adjuvant tamoxifen therapy more closely.

A retrospective analysis of the BIG 1-98 (Breast International Group 1-98) prospective, randomized, double-blind study was reported by Leyland-Jones and colleagues.[18] In BIG 1-98, 8,010 postmenopausal women with hormone receptor–positive early breast cancer were randomized to 5 years of tamoxifen, letrozole, or a sequence of the 2 agents. *CYP2D6* genotyping was conducted in 4,628 patients; individuals were grouped into 3 *CYP2D6* phenotype categories—poor, intermediate, or extensive metabolizing—according to the homozygous or heterozygous presence or absence of reduced-function or null-function alleles. This analysis was limited to the 4,786 patients in the monotherapy arms for whom *CYP2D6* genotyping was available. No *CYP2D6* phenotype was found to be associated with any difference in the breast cancer–free interval, the primary study endpoint.

Similarly, Rae and colleagues reported on an analysis of the prospective, randomized, double-blind ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial that compared 5 years of adjuvant anastrozole versus tamoxifen.[19] *CYP2D6* genotype data were obtained from 1,203 patients, with a 10-year follow-up. No association was found between any *CYP2D6* phenotype and the rate of recurrence among either tamoxifen-treated or anastrozole-treated patients.

Therefore, it is evident that any potential role of the *CYP2D6* genotype on clinical outcomes in tamoxifen-treated patients remains to be elucidated. Data from these abstracts suggest that if any relationship exists, it is weaker than that previously reported. Thus, these studies underscore the fact that there is currently no role for standard testing of *CYP2D6* as a decision tool for whether or not to recommend tamoxifen as adjuvant endocrine therapy. Although not necessarily practice-changing, these results could have an important implication for physicians who are already beginning to use this test in their clinical practice.

Neoadjuvant Treatment

Several very exciting trials evaluating biologic therapy in neoadjuvant treatment of early breast cancer were reported. Many of the investigators behind these studies are interested in the identification of biomarkers or other tumor changes following neoadjuvant treatment that will allow more selective individualization of treatment. This series of biologically-driven studies perhaps implies that we are better learning how to care for patients in the neoadjuvant setting. With validation in larger trials, there will

likely be an even greater push to incorporate neoadjuvant treatment as a model of therapy.

Untch and colleagues reported the primary efficacy endpoint analysis of the German GeparQuinto study (GBG 44), which compared the 2 HER2-targeted agents trastuzumab and lapatinib when given with anthracycline and taxane-based chemotherapy in the neoadjuvant setting.[20] Patients (N=597) with untreated HER2-positive early breast cancer were treated with 4 cycles of 90 mg/m^2 epirubicin plus 600 mg/m^2 cyclophosphamide given every 3 weeks followed by 4 cycles of 100 mg/m^2 docetaxel; patients were randomized to receive this neoadjuvant chemotherapy in combination with either 6 mg/kg (loading dose 8 mg/kg) trastuzumab every 3 weeks or 1,000–1,250 mg/day lapatinib throughout all cycles. The pathologic complete response rate was higher in the trastuzumab arm compared with the lapatinib arm (31% vs 22%), suggesting that trastuzumab may have a greater benefit in the neoadjuvant treatment setting.

In a partner study, von Minckwitz and colleagues reported the primary efficacy endpoint analysis in patients (N=1,889) with untreated HER2-negative early breast cancer who received 4 cycles of 90 mg/m^2 epirubicin plus 600 mg/m^2 cyclophosphamide given every 3 weeks followed by 4 cycles of 100 mg/m^2 docetaxel with or without concomitant 15 mg/kg bevacizumab every 3 weeks added to the chemotherapy cycles.[21] The addition of bevacizumab did not result in an improvement in the pathologic complete response rate, although there was a trend toward increased benefit among patients with triple-negative disease.

Baselga and colleagues presented the first analysis of the NeoALTTO (Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation) trial (BIG 01-06/EGF 106903), a randomized, open-label, neoadjuvant phase III study of lapatinib, trastuzumab, or their combination plus paclitaxel in patients with HER2-positive early breast cancer.[22] Patients (N=455), stratified by tumor size, hormone receptor status, nodal status, and whether they had undergone breast conservation surgery, were randomized to receive 6 weeks of 1,500 mg/day lapatinib, 2 mg/kg (4 mg/kg loading dose) trastuzumab weekly, or a combination of the 2 agents. After this regimen, all patients received additional neoadjuvant treatment with 80 mg/m^2 paclitaxel weekly (lapatinib reduced to 750–1,000 mg/day when combined with paclitaxel) up to week 18, after which they underwent surgery. Following surgery, patients received adjuvant chemotherapy followed by their same induction biologic regimen given for 34 weeks. This current analysis included data up to the time of surgery. The rates of pathologic complete response in the combination, trastuzumab, and lapatinib arms were 51.3%, 29.5%, and 24.7%, respectively (HR, 1.74; P=.0001, for combination vs trastuzumab arms). Combination therapy was also associated with a significant increase in the rate of overall response compared with either single agent. Lapatinib was associated with an increased frequency of diarrhea, hepatotoxicity, and skin disorders, regardless of whether it was given as a single-agent or in combination.

Gianni and colleagues reported an efficacy and safety analysis of the NeoSphere (Neoadjuvant Study of Pertuzumab and Herceptin in an Early Regimen Evaluation) study, a randomized phase II trial evaluating neoadjuvant treatment with trastuzumab and the second-generation HER2-targeting antibody pertuzumab.[23] Patients (N=417) with HER2-positive early-stage breast cancer were randomized to 1 of 4 neoadjuvant treatment arms: docetaxel plus trastuzumab; docetaxel plus pertuzumab; trastuzumab plus pertuzumab; or docetaxel, trastuzumab, and pertuzumab (3-week cycles in all arms: pertuzumab given at a dose of 420 mg [840 mg loading dose], trastuzumab given at a dose of 6 mg/kg [8 mg/kg loading dose], and docetaxel given at a dose of 75 mg/m^2 [increased to 100 mg/m^2 if well tolerated]). Following surgery, all patients received adjuvant chemotherapy with trastuzumab for 1 year. The rates of pathologic complete response were highest among patients who received anti-HER2 combination treatment (docetaxel, trastuzumab, and pertuzumab: 45.8%; docetaxel plus trastuzumab: 29.0%; docetaxel plus pertuzumab: 24.0%; and trastuzumab plus pertuzumab: 17.8%; P=.014 for comparison of docetaxel, trastuzumab, and pertuzumab vs docetaxel plus trastuzumab; P=.031 for docetaxel plus trastuzumab vs trastuzumab plus pertuzumab). The clinical objective response rate followed the same trend (88%, 80%, 71%, and 68%, respectively).

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Management of Advanced Breast Cancer

Clifford Hudis, MD

Each year at the SABCS, a range of new clinical data is presented. Although some years these results may represent novel observations and practice-changing breakthroughs, other years bring data that fill in knowledge gaps and increase the depth of our understanding of advanced and metastatic breast cancer. Data at the 2010 SABCS meeting largely comprised this second category, with a few notable exceptions.

Advances in Cytotoxic Chemotherapy

For many years, palliative chemotherapy has played a key role in the management of patients with incurable metastatic breast cancer. For some patients, like those with triple-negative disease, chemotherapeutic agents are the only choice of therapy, as their disease will not respond to the targeted agents that have made such an impact in hormone receptor–positive and HER2-positive disease. However, it is not only in the setting of triple-negative breast cancer that chemotherapy has a role—even patients with hormone receptor–positive or HER2-positive metastatic breast cancer will ultimately lose response to the targeted agents and consequently require palliative chemotherapy. For this reason, one important focus of research is the development of more effective and less toxic chemotherapeutic agents for patients with advanced disease.

An important and potentially practice-changing abstract describing the EMBRACE (Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389) study, by Vahdat and colleagues, was reported at the SABCS meeting and subsequently published in

The Lancet.[1,2] The publication included data from patients (N=762) throughout the world (region 1: North America, western Europe, Australia; region 2: eastern Europe; and region 3: Latin America, South Africa). The SABCS abstract, however, focused only on an analysis of survival outcomes in the region 1 patient subset (N=488), which comprised a majority (64%) of the overall patient set. The EMBRACE study evaluated the novel chemotherapeutic agent eribulin mesylate, a nontaxane microtubule inhibitor that leads to cancer cell apoptosis.

EMBRACE was an open-label, phase III, clinical trial that randomized patients in a 2:1 fashion to receive either eribulin (1.4 mg/m^2 on days 1 and 8 of a 21-day cycle) or treatment of physician's choice (TPC). All patients had locally recurrent or metastatic breast cancer and had received between 2 and 5 prior lines of chemotherapy (≥2 for advanced disease), which included an anthracycline and a taxane. In the overall study population, the vast majority (96%) of patients in the TPC arm received single-agent chemotherapy; only 4% received hormonal therapy. The use of TPC as the control arm in this trial is significant, allowing eribulin to be compared directly against what study physicians considered to be the best currently available therapy for their individual patients. The primary study endpoint was OS; secondary endpoints included progression-free survival (PFS), objective response rate, and duration of response.

In this region 1 subset analysis, the most common agents administered in the TPC arm (N=163) included vinorelbine (28%), taxanes (20%), gemcitabine (17%), capecitabine (13%), and anthracyclines (12%). A total of 325 patients were randomized to the eribulin arm. The median OS in the region 1 subset was significantly prolonged among eribulin-treated patients compared with TPC-treated patients (13.3 vs 10.2 months; HR, 0.724; 95% CI, 0.568–0.924; *P*=.009). The median PFS, assessed by independent review, was also increased with eribulin (3.3 vs 2.2 months; HR, 0.843; 95% CI, 0.666–1.066; *P*=.153) although the difference did not reach statistical significance.

Importantly, this abstract demonstrated a significant improvement associated with eribulin in OS, a particularly difficult endpoint to achieve. Of interest is the fact that, in this patient subset, while the difference achieved in OS was statistically significant, the increase in PFS was more modest and failed to achieve significance. A gold standard endpoint, OS is not subject to the same debate and controversy commonly applied to the use of PFS and response rate as a clinical trial endpoint, thus making these results particularly robust.[3,4] Thus, the EMBRACE study in particular has set a relatively high expectation for future clinical studies, challenging the widespread notion that survival cannot be improved in the setting of advanced metastatic disease.

Based on the results of the overall EMBRACE study, eribulin received US Food and Drug Administration (FDA) approval in late 2010, with an indication for the treatment of metastatic breast cancer patients who have previously received at least 2 chemotherapeutic regimens for the treatment of metastatic disease.[5] Prior chemotherapy exposure should include an anthracycline and a taxane, either in the adjuvant or metastatic setting.

In another chemotherapy-related abstract, Lalla and colleagues presented the findings of a systematic review of published evidence for treating metastatic breast cancer patients after the second line of therapy.[6] Importantly, this question has also been addressed in previous studies. For example, a 2002 review of multiple clinical studies concluded that evidence-to-date did provide limited support for the use of third-line chemotherapy in selected metastatic breast cancer patients.[7] However, there were no data that demonstrated a clear potential benefit for treatment beyond the third-line setting. In a separate prospective evaluation of health-related quality of life and health-related costs, it was found that in spite of low response and little difference in survival, many women who receive third-line chemotherapy maintain or improve their health-related quality of life.[8] However, the authors of that assessment noted that this effect may not be due to the chemotherapy alone, and instead may be attributed to a placebo-type effect or even a shift in the patient's frame of reference regarding health-related quality of life. Another study investigated the factors that determined metastatic breast cancer patient outcomes following third-line chemotherapy, finding that the response to previous chemotherapy was the only independent variable predicting response and survival following third-line treatment.[9]

In this current study, Lalla and colleagues performed a systematic search of published literature databases, including Medline, EMBASE, and Cochrane, as well as selected conference proceedings from the prior 3–5 years.[6] Only studies that reported efficacy data for third-line or later treatment of metastatic breast cancer patients (≥10) were included, and most of the studies reported a subgroup analysis of a mixed treatment-line population. A total of 29 separate trials were identified, which reported results with 22 different treatment regimens. The majority of these (76%) were single-arm studies; only 1 randomized controlled trial was included. The authors noted that HER2 status and prior exposure to HER2-targeted agents may have a significant impact on late-line treatment. None of the studies identified reported results specific for the HER2-negative patient population, and 21% of the studies specifically investigated treatment of HER2-positive patients.

Overall, the authors found that there was no standard therapeutic regimen used in the third-line and beyond treatment setting. The most commonly reported

patient outcome in the identified studies was overall response rate (ORR); with few exceptions, these patients achieved partial responses. In contrast, OS and PFS were only rarely reported. Among the studies that contained a mixed HER2-status population, the highest ORRs in third-line and later treatment were associated with mitomycin C and capecitabine. Specifically, among 5 studies that evaluated a HER2-positive metastatic breast cancer population, the investigational agent trastuzumab-DM1 (T-DM1) was associated with the highest ORR (38%) in a study of 112 patients.[10] The remaining studies all reported lower response rates, each with a trastuzumab-based chemotherapy regimen. Two studies evaluated capecitabine plus trastuzumab, reporting an ORR of 18% and 21% in 38 and 19 patients, respectively.[11,12] One trial evaluated the combination of gemcitabine plus trastuzumab, with an 11% ORR reported among a total of 18 patients.[13] A fifth study, which evaluated multiple trastuzumab-based chemotherapy regimens, reported no response in 16 patients.[14]

This study highlights an important limitation that is inherent to retrospective studies and cross-study comparisons. During analysis, it is extremely difficult to factor in all of the confounding variables that may have influenced the treatment selection, which, for example, may have biased the high ORRs achieved with mitomycin C and capecitabine. Thus, the best way to truly assess the value of third-line and later therapies would be to conduct a prospective study. Although the results of this systemic review were intriguing, they are not yet relevant to extrapolate to decisions in the clinical setting.

Changing Role of Bevacizumab

Bevacizumab, a monoclonal antibody directed against the vascular endothelial growth factor (VEGF), was the focus of a number of SABCS abstracts. The use of bevacizumab in breast cancer, currently indicated only in the metastatic setting, has recently fallen under intense debate based on cumulative evidence demonstrating a lack of OS improvements but a greater risk for serious adverse events.

Studies presented at SABCS focused on the evaluation of bevacizumab in a variety of breast cancer settings. Some, such as the randomized phase III GeparQuinto trial, demonstrated that bevacizumab combined with chemotherapy offered no benefit over chemotherapy alone in the neoadjuvant treatment of early breast cancer.[15] Other studies focused on the use of bevacizumab in metastatic breast cancer. For example, preliminary results of the open-label phase II AVALUZ (Breast Cancer Treated with Bevacizumab in Combination with Paclitaxel and Gemcitabine as First Line Therapy) trial were reported, suggesting that the combination of bevacizumab with paclitaxel and gemcitabine was active as a first-line regimen in HER2-negative recurrent or metastatic breast cancer patients.[16]

In another study, Carpenter and colleagues tested the efficacy and safety of the combination of 10 mg/kg bevacizumab every 2 weeks for 9 doses, given concurrently with a sequential neoadjuvant chemotherapy regimen of 25 mg/m^2 liposomal doxorubicin every 2 weeks for 3 doses, followed by 175 mg/m^2 paclitaxel every 2 weeks for 3 doses, followed by 600 mg/m^2 cyclophosphamide every 2 weeks for 3 doses.[17] A total of 32 patients with HER2-negative locally advanced invasive breast cancer were enrolled in the study; 3 patients withdrew during treatment. Adjuvant endocrine therapy was administered to hormone receptor–positive patients, and adjuvant bevacizumab was given for 1 year to patients who achieved less than a pathologic complete response after surgery. A total of 24 patients received radiotherapy following their resection.

Throughout the study, no cases of clinical congestive heart failure occurred. The left ventricular ejection fraction was greater than 55% in all patients after completion of the neoadjuvant therapeutic treatment. Of all adverse events observed, the most severe were grade III in intensity, including 7 cases of hypertension and 1 case of skin toxicity (palmar plantar erythrodysesthesia). The remaining toxicities were grade I/II in severity. A total of 5 patients experienced delayed wound healing following surgery.

Thirty patients remained free of recurrence following surgical resection, and a pathologic complete response was achieved in 9 patients. The remaining patients received adjuvant bevacizumab. After a median follow-up of 21 months (range: 12–33), none of the 30 patients who successfully completed neoadjuvant treatment, surgical resection, and radiotherapy had experienced a local or distant recurrence. The median OS and median PFS, both calculated from diagnosis, was 21.7 months (range: 10.7–35.8) and 21.7 months (range: 9.6–35.8), respectively. These outcomes were relatively similar between hormone receptor–positive and hormone receptor–negative patients.

Although the combination of bevacizumab with sequential neoadjuvant chemotherapy was found to be relatively well tolerated, it did not result in a great impact on the rate of pathologic complete response following surgery. Overall, this was a small and nonrandomized study, limiting the conclusions we can draw regarding the efficacy of this combination. However, these results may lay the groundwork for the design of future clinical studies.

Targeting HER2 Disease

The HER2-positive breast cancer patient population has been the subject of intense attention and focused research for over a decade. The recognition of HER2 expression in

breast tumors and an increased understanding of its role in the underlying biology of disease led to the development of the anti-HER2 targeted monoclonal antibody trastuzumab. Pivotal trials have validated the efficacy of trastuzumab in both the first-line treatment of metastatic disease and as a component of adjuvant therapy.[18-22] These trials were practice-changing, and HER2-positive breast cancer patients now have a better prognosis than those with HER2-negative disease.[23] However, much remains to be learned regarding the optimal treatment of HER2-positive breast cancer; several studies presented at SABCS reported on developments in this area.

Halyard and colleagues assessed the impact of adjuvant trastuzumab therapy on the risk of local regional recurrence.[24] This study evaluated the rates of local regional recurrence—an important indicator of an increased risk for developing metastatic disease—in patients enrolled in the phase III NCCTG N9831 (North Central Cancer Treatment Group N9831) trial.[19] The NCCTG N9831 trial enrolled patients (N=3,505) with high-risk HER2-positive breast cancer; all patients underwent lumpectomy plus radiotherapy, mastectomy alone, or mastectomy plus radiotherapy. For adjuvant therapy, patients were randomized to 1 of 3 treatment arms: doxorubicin/cyclophosphamide followed by paclitaxel; doxorubicin/cyclophosphamide followed by paclitaxel followed by trastuzumab; or doxorubicin/cyclophosphamide followed by paclitaxel/trastuzumab followed by trastuzumab. This current analysis consisted of 2,816 patients who were eligible for a risk analysis of local regional recurrence as a first event, with a median follow-up of 5.3 years. The 5-year local regional recurrence rate was 4.1% (95% CI, 3.5–4.9), and was relatively similar regardless of what type of surgical resection the patient underwent. Inclusion of trastuzumab in adjuvant therapy was associated with a modest and nonsignificant reduction in the risk of local regional recurrence among patients who underwent either lumpectomy plus radiotherapy (HR, 0.63) or mastectomy plus radiotherapy (HR, 0.51), but not mastectomy alone (HR, 1.93). Although these results suggest that adjuvant trastuzumab may have an additive effect with radiotherapy for decreasing the risk of local regional recurrence, they should be interpreted with caution, especially in light of the smaller number of patients who underwent mastectomy alone. Regardless, this study provides a baseline for future investigation of the potential of radiosensitization by trastuzumab.

One of the most significant questions addressed regarding HER2-positive breast cancer was the value of continuing trastuzumab in patients who experienced disease progression on trastuzumab. Studies evaluating the efficacy of the alternative anti-HER2 agent lapatinib in combination with capecitabine have demonstrated there is a benefit to continued HER2 targeting even in patients who had progressed on trastuzumab therapy.[25-27]

The TBP (Treatment Beyond Progression; GBG 26/BIG 3-05) prospective, randomized, phase III trial was conducted to determine the benefit of combining trastuzumab (6 mg/kg every 3 weeks) with capecitabine (2,500 mg/mg^2 on days 1–14 of a 21-day cycle) versus the same capecitabine dose alone in metastatic breast cancer patients (N=156) who had experienced disease progression while on trastuzumab.[28] Due to both poor enrollment and the approval of lapatinib for the treatment of HER2-positive patients who had progressed on trastuzumab, the study was closed early. Initial results of the TBP trial demonstrated a significant improvement in both the ORR with the combination versus single-agent treatment (48.1% vs 27.0%; odds ratio 2.50; *P*=.0115) as well as the median time to progression (8.2 vs 5.6 months; HR, 0.69; 95% CI, 0.48–0.97; *P*=.0338). Importantly, this benefit was found to occur without a concurrent increase in toxicity.

In an update of the TBP trial, von Minckwitz and colleagues reported the final OS analysis after a median follow-up of 20.7 months.[29] The median OS was similar in the trastuzumab plus capecitabine group compared with the capecitabine-only group (24.9 vs 20.6 months, HR, 0.94, 95% CI, 0.65–1.35; *P*=.73). In a multivariate analysis, performance status, hormone receptor status, and metastatic site were all identified as independent prognostic factors for OS. However, there was no difference in the OS among patients who had achieved a clinical response or a clinical benefit to therapy. In a post-hoc analysis, among the subset of patients (N=52) who had continued or reinitiated anti-HER2 therapy following a second progression, the OS was prolonged compared with the patient subset (N=88) that did not receive third-line anti-HER2 treatment (18.8 vs 13.3 months; HR, 0.63; *P*=.02).

In a related study, Waddell and colleagues retrospectively evaluated the efficacy and safety of continuing trastuzumab therapy in patients (N=114) with HER2-positive metastatic or locally advanced breast cancer who had progressed on trastuzumab treatment. They reported on the experience in a single-center clinical population of unselected individuals.[30] The median time to progression was 24 weeks (95% CI, 21–28 weeks), and the median OS was 19 months (95% CI, 12–24 months), both of which were comparable to the rates reported in prior studies of both continued trastuzumab and continued lapatinib.[25,28] Thus, the investigators concluded that continued trastuzumab beyond disease progression was justified in HER2-positive patients with advanced disease.

Studies evaluating 2 investigational HER2-targeted agents were also reported at the SABCS meeting.

T-DM1 is a novel antibody-drug conjugate composed of trastuzumab linked to the cytotoxic antimicrotubule agent DM1, a derivative of maytansine.[31] T-DM1 has shown promising activity in both phase I and phase II trials, and it was most recently demonstrated to have similar efficacy but an improved toxicity profile compared with standard trastuzumab when combined with docetaxel for first-line treatment of metastatic disease.[32-34] A second novel agent in development, pertuzumab, is a recombinant anti-HER2 monoclonal antibody that targets a binding site on HER2 that is unique from that recognized by trastuzumab. A phase II trial showed a benefit of pertuzumab when combined with continued trastuzumab in HER2-positive metastatic breast cancer patients who had progressed on prior trastuzumab therapy.[35] Based on preclinical evidence that suggested a potential synergistic relationship between pertuzumab and T-DM1,[36] 2 studies were reported at SABCS that investigated this combination in patients.

Diéras and colleagues presented results from the TDM4373G study, an international, single-arm, phase Ib/II clinical trial that evaluated the safety and efficacy of the T-DM1 plus pertuzumab in HER2-positive locally advanced or metastatic breast cancer.[37] The majority of patients enrolled had relapsed disease (N=46), including all patients with locally advanced breast cancer; approximately one-third of patients had previously untreated disease (N=21), all with metastatic breast cancer. During the phase Ib dose-escalation portion of this trial, which was previously reported, an optimal dosing schedule was established of 3.6 mg/kg T-DM1 and an 840 mg loading dose/420 mg maintenance dose of pertuzumab, both administered every 3 weeks.[38] An objective response of 34.8% (95% CI, 22.2–50.0) was reported among patients with recurrent disease; this rate was increased to 57.1% (95% CI, 34.0–78.2) among patients with previously untreated disease. Most of these were partial responses, although 2.2% and 9.5% of patients with recurrent or previously untreated disease, respectively, achieved a complete response. The most frequent grade 3 or higher adverse events included fatigue (11.9%) and thrombocytopenia (11.9%). A total of 29.9% of patients experienced a serious adverse event. Although this was a small, nonrandomized study, the results were promising and showed clinical activity and a well tolerated safety profile in response to the combination of these novel agents.

Krop and colleagues presented the dose-escalation phase Ib TDM4652G study involving the combination of T-DM1 with both pertuzumab and paclitaxel in HER2-positive patients (N=21) with locally advanced or metastatic breast cancer who had previously received treatment with a trastuzumab-containing regimen.[39] Using a 3+3 study design, patients were treated in a first phase with T-DM1 (every 3 weeks) and paclitaxel (every week); this was followed by a second phase in which pertuzumab was added to the maximum tolerated dose of T-DM1/paclitaxel established. In this report, only data from the first 14 patients enrolled in the first phase of this study (T-DM1 plus paclitaxel) were reported. These patients were heavily pretreated, with a median of 10 (range: 5–23) prior systemic therapies excluding hormonal therapy. All of the patients had received prior trastuzumab, and most had received prior taxane and lapatinib as well. A median of 4.5 (range: 1–10) doses of T-DM1 and 11 (range: 1–29) doses of paclitaxel were administered. In the first treatment cohort (2.4 mg/kg T-DM1 and 65 mg/m^2 paclitaxel), 2 patients experienced a dose-limiting toxicity (grade 3 aspartate aminotransaminase/alanine aminotransferase elevation and grade 3 dehydration secondary to nausea/vomiting). The second treatment cohort was thus given a lower T-DM1 dose (2.0 mg/kg T-DM1 and 65 mg/m^2 paclitaxel); patients in this group experienced no dose-related toxicities. The final treatment cohort received a higher paclitaxel dose (2.0 mg/kg T-DM1 and 80 mg/m^2 paclitaxel), but 1 patient experienced a dose-limiting toxicity (grade 3 neutropenia). The final maximum tolerated dose established was 2.0 mg/kg T-DM1 and 80 mg/m^2 paclitaxel. Overall, 6 serious adverse events in 3 patients were observed; 3 of these were considered related to treatment (grade 2 vomiting, grade 3 dehydration, grade 3 hypersensitivity). Paclitaxel only was discontinued in 6 patients due to adverse events, and 1 patient discontinued treatment altogether due to toxicity (grade 2 thrombocytopenia). Overall, 2 confirmed objective responses and 4 unconfirmed partial responses were reported.

Both of these studies involving the investigational agents T-DM1 and pertuzumab are encouraging, and suggest that in the future it may be possible to treat patients with a minimally toxic regimen including or consisting of biologic therapy. Future development of these agents is ongoing; for example, the results of the phase III CLEOPATRA (Clinical Evaluation of Pertuzumab and Trastuzumab) trial, which is investigating the addition of pertuzumab to trastuzumab plus docetaxel in previously untreated HER2-positive metastatic breast cancer, are eagerly awaited.[40]

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New Biomarkers for Intervention in Breast Cancer

Edith Perez, MD

Breast cancer is a very complex and heterogeneous disease; fortunately, the underlying biology of breast cancer is better understood now more than ever. In recent years, the main biologic targets that have been used to guide therapeutic decisions have been restricted to the hormone receptors (ER and/or PR) and HER2. However, it is important to realize that even though use of these 3 markers is considered a standard of care for guiding adjuvant therapy in early breast cancer, the therapies that target each are far from perfect. In fact, they rarely completely eradicate the disease.

Therefore, as we consider novel targets for therapeutic interventions, 2 main issues should be considered. First, should the agent directed against the novel target be used in combination with current ER/PR- and HER2-targeted strategies? Second, what are the other targets (aside from ER/PR and HER2) that may be worthy of single-agent drug development?

Biomarkers for Therapeutic Targeting

Biomarkers to be identified may involve a number of different processes, including gene expression, protein expression, and protein phosphorylation. Identification of these novel targets may be made in both preclinical studies as well as through appropriate biomarker analysis in tumor specimens. This latter technique will help to establish whether the biomarker is or is not abnormally present as well as help to attribute any functional activity of the biomarker (such as affecting the tumor growth pattern and/or sensitivity to treatment). Through these investigations, specific targets have emerged as potentially exciting in the setting of early breast cancer, including the insulin-like growth factor receptor, the mammalian target of rapamycin, and the phosphoinositide 3-kinase, as well as myriad potential targets within the apoptotic and VEGF pathways.

Circulating Tumor Cells

In addition to their potential as novel therapeutic targets, newly discovered biomarkers may also serve as surrogate indicators that may be developed for use in clinical trials and ultimately for drug approval. These include both imaging-based biomarkers and, potentially, circulating tumor cells (CTCs). One of the main questions related to the use of CTCs, especially in the context of biomarker utility, is whether those tumor cells in the circulation share the same molecular profile as the tumor cells that are responsible for invasion and metastasis. Although CTCs are especially appealing, much work is required before it will be determined if they may have day-to-day applicability in clinical practice.

At the 2010 SABCS, Rack and colleagues presented a translational study of patients enrolled in the SUCCESS (Simultaneous Study of Docetaxel-Gemcitabine Combination Adjuvant Treatment, as well as Extended Bisphosphonate and Surveillance-Trial) trial.[1] This prospective, open-label, phase III trial randomized patients (N=2,026) to 2 different adjuvant therapy regimens (fluorouracil, epirubicin, cyclophosphamide [FEC] plus docetaxel versus FEC plus docetaxel and gemcitabine, each followed by endocrine therapy plus 2 vs 5 years of zoledronic acid). All patients had either node-positive or high-risk node-negative early breast cancer. This particular analysis evaluated the prognostic significance of CTCs in patients participating in this trial. Prior to the initiation of adjuvant therapy, CTCs were detected in 21.5% of patients (≥1 CTC considered positive). Notably, positive CTC detection compared with negative CTC detection was significantly associated with worse 3-year DFS (88.1% vs 93.7%; $P<.0001$), worse 3-year distant DFS (87.9% vs 94.2%; $P<.0001$), and worse 3-year OS (93.2% vs 97.3%; $P=.0002$). In a multivariate analysis, positive CTC detection was associated with a poor DFS (HR, 1.878; 95% CI, 1.318–2.676; $P=.0005$) and a poor OS (HR, 1.907; 95% CI, 1.142–3.183; $P=.0136$). The risk of poorer DFS or OS increased with higher numbers of CTCs found (DFS: 5 vs 0–4 CTCs: HR, 4.035, $P<.05$; OS: 5 vs 0–4 CTCs: HR, 3.051, $P<.05$). Thus, this study attributes a significant prognostic value to CTCs in the peripheral blood of patients with early breast cancer prior to their initiation of adjuvant chemotherapy.

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Dr. Perez has no real or apparent conflicts of interest to report.

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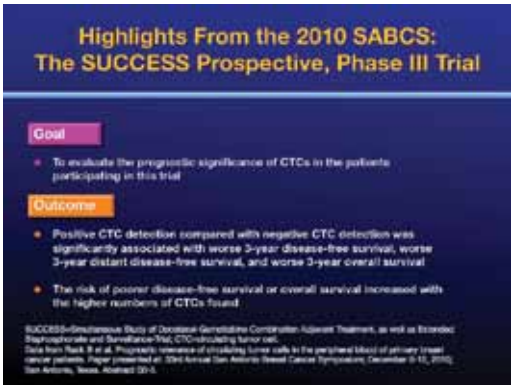

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