

Highlights in Metastatic Breast Cancer From the 2011 San Antonio Breast Cancer Symposium (SABCS)

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Special Reporting on:

- Everolimus for Postmenopausal Women With Advanced Breast Cancer
- The Addition of Pertuzumab to Trastuzumab and Docetaxel in Patients With Previously Untreated HER2-Positive Metastatic Breast Cancer
- Neoadjuvant Pertuzumab and Trastuzumab With or After an Anthracycline-Containing or Anthracycline-Free Standard Regimen
- Neoadjuvant Pertuzumab and Trastuzumab: Biomarker Analyses
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- Trials of Bisphosphonates in Breast Cancer

PLUS Meeting Abstract Summaries

With Expert Commentary by:

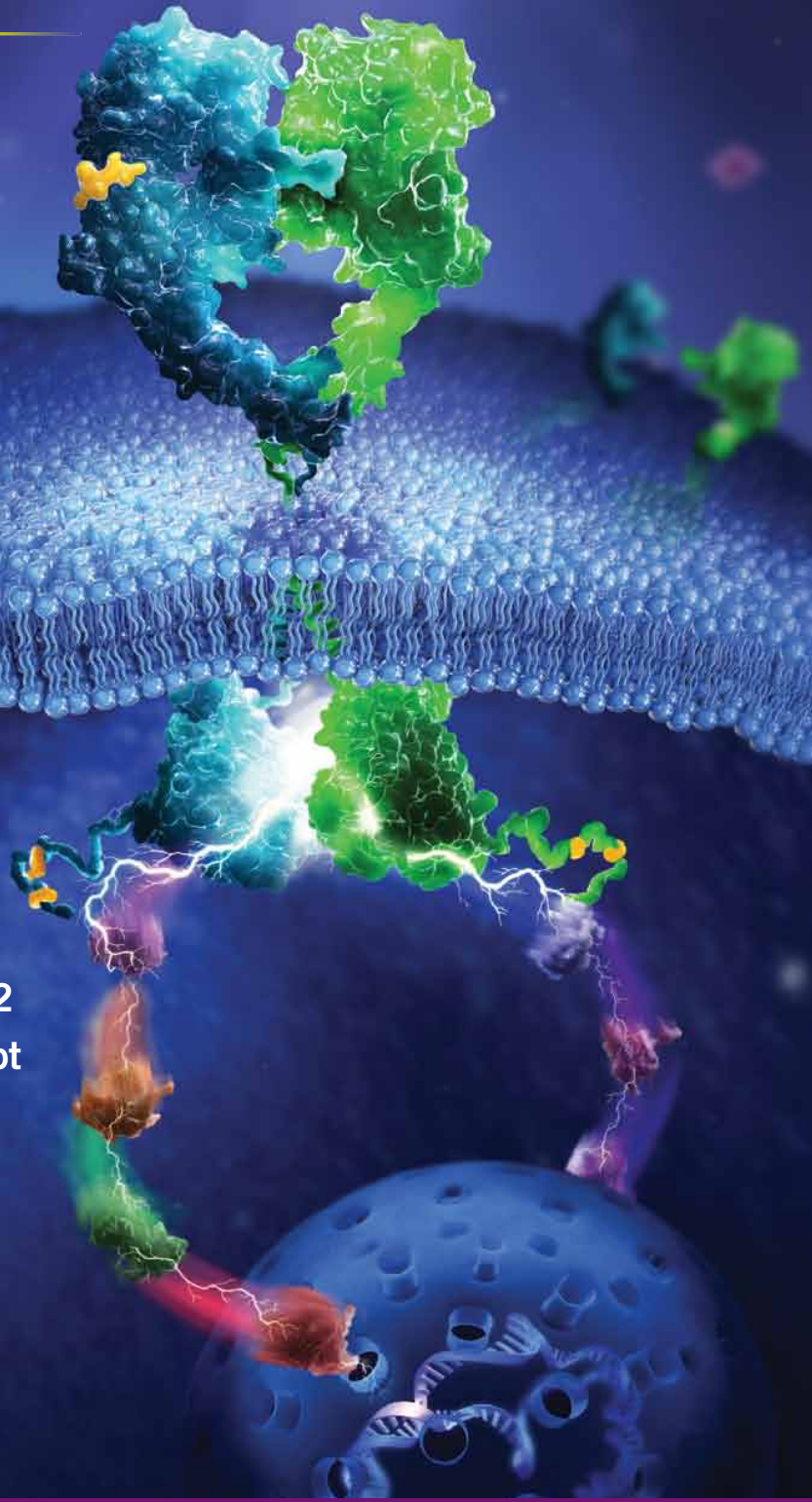
Charles L. Vogel, MD

Professor of Clinical Medicine
Sylvester Comprehensive Cancer Center at Deerfield
Miller School of Medicine, University of Miami
Miami, Florida and
Clinical Director
Cancer Research Network
Deerfield Beach, Florida

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In HER2+ breast cancer
**HER2 dimerization activates
downstream signaling.**

**What if you could inhibit HER2
dimerization and further disrupt
the oncogenic cascade?**



The potential of HER2 Dimerization Inhibitors (HDIs)

HER2 dimerization: an important driver of HER2+ disease

Despite significant treatment advances, HER2+ breast cancer continues to be a challenging disease requiring aggressive intervention.

HER dimerization, or receptor pairing, is a critical driver of tumor growth in HER2+ disease.^{1,2}

The HER family of receptors is composed of 4 receptors that must pair, or dimerize, in order to activate downstream signaling.³

When HER2 receptors are overexpressed, as in HER2+ breast cancer, excessive dimerization is thought to lead to abnormal activation of signaling, which results in tumor growth.^{1,3}

The HER2:HER3 dimer: the most potent oncogenic HER dimer

Although HER2 can dimerize with any HER family member, preclinical studies suggest that the HER2:HER3 dimer is the most potent oncogenic HER receptor pair,¹ as it activates 2 key pathways.^{2,4} While HER2 activates the MAPK pathway, HER3 is the only receptor that can directly activate the PI3K pathway.^{2,5} The HER2:HER3 dimer may be crucial for the aggressive tumor growth seen in HER2+ breast cancer.^{2,4}

HER2



Causes cell proliferation by activating the MAPK (mitogen-activated protein kinase) pathway^{2,5}

HER3



Leads to cell survival signaling by activating the PI3K (phosphatidylinositol 3-kinase) pathway^{2,5}

HER2 Dimerization Inhibitors (HDIs): the potential for a more comprehensive blockade

Preclinical studies demonstrate that inhibiting HER2 dimerization, including the HER2:HER3 dimer, interrupts both the MAPK and PI3K pathways and, ultimately, tumor growth.⁶

Inhibition of ligand-induced HER2 dimerization while administering other HER2-targeted agents may offer a more comprehensive blockade of signaling in HER2+ disease.⁷

Learn more about the potential of HDIs in HER2+ breast cancer

Scan to visit ResearchHDIs.com to explore more and view a narrated video.



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Everolimus for Postmenopausal Women With Advanced Breast Cancer: Updated Results of the BOLERO-2 Phase III Trial

At the 2011 San Antonio Breast Cancer Symposium (SABCS), Hortobagyi and colleagues presented results of the phase III BOLERO-2 (Breast Cancer Trials of Oral Everolimus) clinical trial with 12 months of patient follow-up.¹ The study examined the efficacy and safety of everolimus in postmenopausal patients with hormone receptor–positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer that was refractory to prior treatment with nonsteroidal aromatase inhibitors. Hormone receptor–positive breast cancer, including metastatic disease, is currently managed with sequential single-agent endocrine therapy that is changed upon disease progression. However, the benefit decreases with each subsequent line of endocrine therapy, and endocrine resistance eventually develops. The mammalian target of rapamycin (mTOR) signaling pathway has been proposed as a major mediator of endocrine resistance. It was therefore hypothesized that the administration of an mTOR inhibitor combined with estrogen deprivation could overcome mTOR resistance to endocrine therapy.

In a phase II study, 270 postmenopausal patients with newly diagnosed, operable, estrogen receptor

(ER)-positive breast cancer received neoadjuvant treatment with everolimus plus letrozole or letrozole plus placebo.² The response rate for the drug combination was higher than that seen with letrozole alone (68% vs 59%; $P=.062$). A greater antiproliferative response was also observed, with a decrease in the Ki-67 proliferative index in 57% of patients receiving the combination treatment versus 30% of those treated with letrozole plus placebo ($P<.01$). A separate phase II study of 111 postmenopausal patients with ER-positive advanced breast cancer that was previously treated with an aromatase inhibitor compared tamoxifen plus everolimus to tamoxifen alone.³ Exploratory analyses showed that the addition of everolimus conferred significant improvement in progression-free survival (PFS; 8.6 months vs 4.5 months; hazard ratio [HR], 0.54; $P=.0021$) and overall survival (OS; HR, 0.45; $P=.007$).

In light of these results, the international, double-blind, placebo-controlled, phase III BOLERO-2 study was designed to examine the impact of adding everolimus to exemestane therapy. The study enrolled 724 postmenopausal women with advanced breast cancer that had recurred or progressed on letrozole or anastrozole.

Patients were randomized 2:1 to receive exemestane 25 mg/day plus everolimus 10 mg/day (485 patients) or exemestane 25 mg/day plus placebo (239 patients). The primary endpoint was PFS, determined by local assessment, and the study was designed to detect a 26% reduction in progression events with 90% power. Secondary endpoints included OS, response rate, quality of life, and safety. The results presented here are based on 457 PFS events after a median follow-up of 12.5 months.

The median age was 62 years, and the 2 treatment arms were well-balanced for baseline characteristics. Most patients (60%) had an excellent performance status, one-third of the patients had liver metastasis, and one-third had lung metastasis. Thirty-six percent had metastasis in at least 3 organ sites. In addition to having experienced prior relapse or progression on letrozole or anastrozole, approximately 50% of the patients had received prior tamoxifen, and 26% had received prior chemotherapy for metastases. More than 50% of patients had received at least 3 prior endocrine therapies.

A higher proportion of patients in the control arm discontinued therapy (90% vs 71%), mainly due to disease progression. Adverse events (8% vs 3%) and consent withdrawal (9% vs 3%) were slightly more frequent in the com-

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bination arm relative to the control arm. The median PFS based on investigator assessment was significantly longer for the everolimus combination treatment (7.4 months vs 3.2 months; HR, 0.44; 95% confidence interval [CI], 0.36–0.53; $P < 1 \times 10^{-16}$). These findings were confirmed by the results from independent central radiology review, which yielded a median PFS of 11 months for patients treated with everolimus plus exemestane and 4.1 months for placebo plus exemestane (HR, 0.36; 95% CI, 0.28–0.45; $P < 1 \times 10^{-16}$). A benefit from the everolimus combination treatment was consistently observed for all prognostic subgroups. The response rate and clinical benefit rate clearly and significantly favored the combination of everolimus plus exemestane. Due to the high level of pretreatment—with over half of the patients receiving protocol therapy as fourth-line treatment—the response rate was modest: 12% for treatment with everolimus versus 1.3% without ($P < .0001$). The rate of clinical benefit was 50.5% versus 25.5%, respectively ($P < .0001$).

At the time of analysis, 137 deaths had been observed, short of the 182 projected for the first interim OS analysis. Fewer deaths occurred in the combination arm (17.2% vs 22.7%). Common adverse events were consistent with those observed in previous everolimus clinical trials. The most common adverse events of any grade occurring in at least 30% of patients treated with the combination were stomatitis (59%), rash (39%), fatigue (36%), diarrhea (33%), and decreased appetite (30%). Grade 3/4 toxicities were uncommon. The most common grade 3/4 adverse events seen in the everolimus plus exemestane group versus the placebo plus exemestane group were stomatitis (8% vs <1%), hyperglycemia (<6% vs <1%), and fatigue (<5% vs 1%). Grade 3 pneumonitis was observed only in patients receiving everolimus (3% vs 0%). Despite the increased rate of toxicities for patients receiving the everolimus combination, quality of life did not differ between the 2 arms.

First Results of AVEREL, a Randomized Phase III Trial to Evaluate Bevacizumab (BEV) in Combination With Trastuzumab (H) + Docetaxel (DOC) as First-Line Therapy for HER2-Positive Locally Recurrent/Metastatic Breast Cancer (LR/mBC)

Gianni presented the results of the phase III AVEREL trial, which was designed to assess the efficacy and safety of treatment with trastuzumab plus docetaxel with or without bevacizumab in previously untreated HER2-positive locally recurrent or metastatic breast cancer (Abstract S4-8). HER2-positive disease was centrally confirmed either by immunohistochemistry or FISH. Patients were randomized 1:1 to receive trastuzumab (8 mg/kg loading followed by 6 mg/kg maintenance) plus docetaxel (100 mg/m²) every 3 weeks, or to receive the same treatment plus bevacizumab (15 mg/kg) every 3 weeks. The 2 antibodies were given until disease progression, and docetaxel administration was planned for a minimum of 6 cycles. The primary endpoint was investigator-assessed PFS, with secondary endpoints to assess safety, efficacy, and patient quality of life. Baseline characteristics were generally well-balanced between the 2 arms, with a median age overall of 54 years. The incidence of visceral metastases was higher in the bevacizumab-containing arm (n=216) compared to the control arm (n=208; 77% vs 71%). By investigator assessment, PFS increased from 15.7 months without bevacizumab to 16.5 months with bevacizumab, but the difference was not statistically significant (HR, 0.82; 95% CI, 0.65–1.02; $P = .0775$). However, the assessment by the independent review committee showed a statistically significant prolongation of PFS with bevacizumab, from 13.9 months to 16.8 months (HR, 0.72; 95% CI, 0.54–0.94; $P = .0162$). Subgroup analysis suggested a PFS benefit in the small number of patients over 65 years of age at baseline (n=77; HR, 0.40; 95% CI, 0.23–0.68). The overall response rate was similar for the 2 arms ($P = .3492$) based on investigator assessment, but it was higher with bevacizumab based on independent review committee assessment (76.5% vs 65.9%; $P = .0265$). Overall survival did not differ between the 2 arms based on interim analysis ($P = .7078$). There were more grade 3–5 adverse events (AEs) in the bevacizumab-containing arm (48.4% vs 38.3%). Specific grade 3–5 AEs of interest that were increased with bevacizumab included cardiac events (5.1% vs 2.9%), febrile neutropenia (11.6% vs 8.7%), and hypertension (11.6% vs 0.5%). In an exploratory biomarker analysis, patients with high initial levels of plasma vascular endothelial growth factor A experienced a greater PFS benefit with bevacizumab than patients with low initial levels of this factor.

Estrogen deprivation induced by aromatase inhibitors such as exemestane has been shown to cause a loss of bone density and increased risk of fractures. To examine the effect of everolimus on these parameters, various bone resorption and formation markers were measured at 0, 6, and 12 weeks. Although the expected

increase in all these markers was observed in the exemestane arm, the levels of these same markers were reduced in the combination arm, suggesting a protective effect. Pharmacokinetic analysis showed that everolimus concentrations were consistent with previous data from single-agent studies. However, exemestane concentra-

tions increased significantly upon concomitant administration of everolimus. The median values of estradiol remained similar between the arms (median 3.88 pg/mL vs 3.07 mg/mL at 4 weeks for the everolimus vs placebo arms, respectively).

Everolimus is the first therapeutic agent that significantly enhances the efficacy of endocrine therapy in patients with hormone receptor–positive, HER2–negative advanced breast cancer. Hortobagyi concluded that the demonstrated superiority of everolimus plus endocrine

therapy compared to endocrine therapy alone represents a paradigm shift in the management of this disease. The international nature of the study, with broad representation of multiple ethnic and cultural groups, underscores the wide applicability of these findings.

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A Phase II, Randomized, Double-Blind, Placebo-Controlled Registration Trial to Evaluate the Efficacy and Safety of Pertuzumab + Trastuzumab + Docetaxel vs. Placebo + Trastuzumab + Docetaxel in Patients With Previously Untreated HER2-Positive Metastatic Breast Cancer (CLEOPATRA)

In patients with metastatic breast cancer, trastuzumab-based therapy improves PFS and OS, yet disease progression still occurs in a majority of patients. Therapy with concomitant pertuzumab and trastuzumab has shown improved activity and a good safety profile in phase II trials of patients with HER2-positive breast cancer previously treated with an anti-HER2 agent.^{1,2}

Pertuzumab and trastuzumab bind to different sites on the HER2 molecule and have complementary mechanisms of action.³ Trastuzumab binds to subdomain IV of the HER2 extracellular domain and exerts its antitumor effect by inhibiting ligand-independent HER2 signaling. It also activates antibody-dependent, cell-mediated cytotoxicity and blocks HER2 extracellular domain shedding. Pertuzumab binds to the HER2 dimerization domain, or subdomain II of the extracellular domain. Thus, pertuzumab binding prevents HER2 from dimerizing with

other receptors of the HER2 family—most notably, HER3. Like trastuzumab, pertuzumab also stimulates antibody-directed cell-mediated cytotoxicity. Based on their different binding sites and complementary mechanisms of action, administration of pertuzumab and trastuzumab together in HER2-positive tumor models increases the blockade of HER2 signaling and produces greater antitumor activity than either agent alone.

The CLEOPATRA (A Study to Evaluate Pertuzumab + Trastuzumab + Docetaxel vs. Placebo + Trastuzumab + Docetaxel in Previously Untreated HER2-Positive Metastatic Breast Cancer) trial was a randomized, double-blind, placebo-controlled phase III study of patients with HER2-positive metastatic breast cancer that investigated the safety and efficacy of combination treatment with trastuzumab and docetaxel, plus either pertuzumab or placebo as first-line therapy.^{4,5} Baselga

and coworkers presented results of the trial, in which patients (N=808) were randomized 1:1 to receive either pertuzumab or placebo, and randomization was stratified based on geographic location and whether the patient had received prior neoadjuvant or adjuvant chemotherapy. For each 3-week cycle, patients received pertuzumab (840-mg loading dose followed by 420 mg maintenance) or placebo, trastuzumab (8-mg/kg loading dose followed by 6 mg/kg maintenance), and docetaxel (75 mg/m²). The docetaxel was escalated to 100 mg/m² if tolerated.

HER2-positive tumor status was centrally confirmed by either immunohistochemistry (IHC) or fluorescence-based in situ hybridization (FISH). All patients had locally recurrent, unresectable, or metastatic breast cancer. Patients were allowed a maximum of 1 form of hormonal therapy prior to randomization. Prior neoadjuvant or adjuvant treatment for breast cancer was allowed if it was

followed by a disease-free interval of at least 12 months. Baseline left ventricular ejection fraction (LVEF) of at least 50% was required, and patients with a history of congestive heart failure or an LVEF decrease to less than 50% after prior trastuzumab therapy were not enrolled.

The trial's primary endpoint was independently-assessed PFS. Secondary endpoints included investigator-assessed PFS, overall response rate (ORR), OS, and safety. The trial required 800 patients and approximately 381 PFS events to provide 80% power to detect a 33% improvement in independently-assessed PFS, with an HR of .75, at the 2-sided significance level of 5%. For OS, 800 patients and 385 OS events were required to provide 80% power to detect a 33% improvement in OS, with an HR of .75 at a 2-sided significance level of 5%. Interim OS analysis was planned at the time of the primary PFS analysis.

Patient baseline characteristics were well-balanced between the 2 treatment arms. Nearly 50% of patients tested positive for the estrogen and/or progesterone receptors, and more than 80% of patients had measurable disease. In the placebo and pertuzumab arms, 47% and 46% of patients, respectively, had received prior neoadjuvant or adjuvant chemotherapy.

After accumulation of 433 events, independently-assessed median PFS improved from 12.4 months in the placebo control arm (406 patients) to 18.5 months in the pertuzumab arm (402 patients; HR, 0.62; 95% CI, 0.51–0.75; $P < .0001$ [Figure 1]). The PFS is the longest reported to date for patients with advanced, HER2-positive breast cancer. The results from the investigator reports overlapped substantially with those from independent assessments—with approximately 85% concordance for each of the treatment arms—and supported the superiority of combined antibody therapy plus docetaxel (HR=0.65; 95% CI, 0.54–0.78; $P < .0001$).

With the exception of patients with nonvisceral disease, most prespecified subgroup analyses showed a benefit

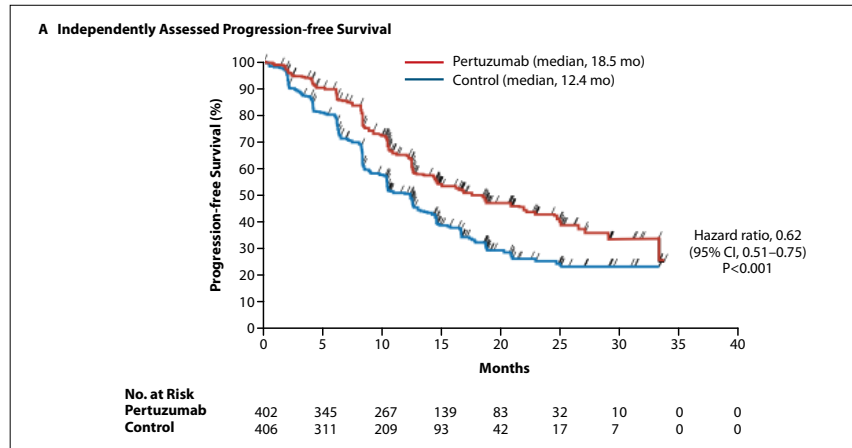


Figure 1. Progression-free survival in the CLEOPATRA trial (A Study to Evaluate Pertuzumab + Trastuzumab + Docetaxel vs. Placebo + Trastuzumab + Docetaxel in Previously Untreated HER2-Positive Metastatic Breast Cancer). Adapted from Baselga J et al. *N Engl J Med.* 2011 Dec 7.⁵

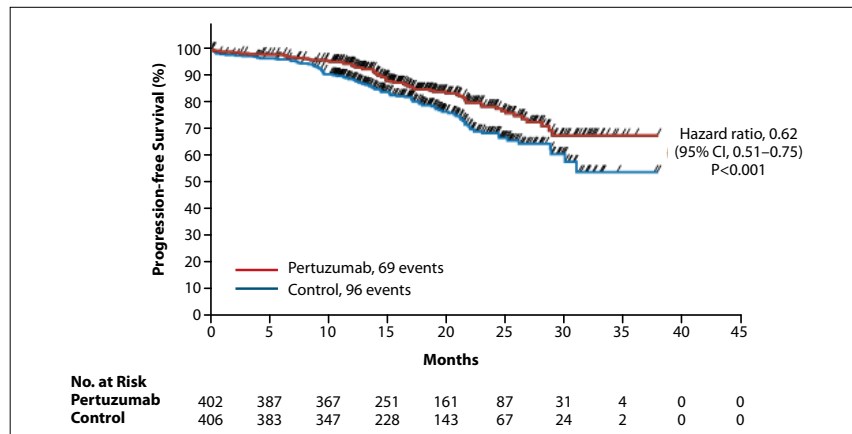


Figure 2. Overall survival in the CLEOPATRA trial (A Study to Evaluate Pertuzumab + Trastuzumab + Docetaxel vs. Placebo + Trastuzumab + Docetaxel in Previously Untreated HER2-Positive Metastatic Breast Cancer). Adapted from Baselga J et al. *N Engl J Med.* 2011 Dec 7.⁵

from treatment that contained pertuzumab. Notably, the benefit seen in patients with hormone receptor-positive disease (388 patients; HR, 0.72; 95% CI, 0.55–0.95) was comparable to that seen in patients with hormone receptor-negative disease (408 patients; HR, 0.55; 95% CI, 0.42–0.72).

Because adjuvant HER2 was not approved until 2006, and trial enrollment began in 2008, relatively few of the enrolled patients had previously received treatment with trastuzumab (88 patients) compared to those who

had not (288 patients). The pertuzumab combination treatment yielded a similar benefit in trastuzumab-naïve patients (21.6 months vs 12.6 months; HR, 0.60; 95% CI, 0.43–0.83) and in patients with prior trastuzumab exposure (16.9 months vs 10.4 months; HR, 0.62; 95% CI, 0.35–1.07). In patients with measurable disease at baseline, the ORR improved from 69.3% in the placebo control arm (336 patients) to 80.2% in the pertuzumab treatment arm (343 patients; $P = .0011$). With a median follow-up of 19.3 months and

165 OS events, the available data suggested a trend toward improved OS for patients in the pertuzumab combination arm (HR, 0.64; 95% CI, 0.47–0.88; $P=.0053$ [Figure 2]). However, the result did not cross the O’Brian-Fleming stopping boundary, and hence the result is considered exploratory. Final OS results are expected in 2013.

The median time on study treatment was 11.8 months for the placebo combination arm (397 patients) and 18.1 months for the pertuzumab combination arm (407 patients). Both arms received a median 8 cycles of docetaxel at a median dose intensity of 25 mg/m² per week.

Cardiotoxicity, as assessed by symptomatic left ventricular systolic dysfunction and LVEF, did not appear to increase for patients exposed to pertuzumab plus trastuzumab and docetaxel relative to the placebo control treatment. Adverse events of any grade that occurred with at least 5% frequency in the pertuzumab combination arm relative to the control arm included diarrhea (66.8% vs 46.3%), rash (33.7% vs 24.2%), mucosal inflammation (27.8% vs 19.9%), febrile neutropenia (13.8% vs 7.6%), and dry skin (10.6% vs 4.3%). Adverse events of grade 3 or higher that occurred with at least 5% frequency in the pertuzumab or placebo arm included neutropenia (48.9% vs 45.8%), febrile neutropenia (13.8% vs 7.6%), leukopenia (12.3% vs 14.6%), and diarrhea (7.9% vs 5.0%).

In summary, CLEOPATRA met its primary endpoint and demonstrated a statistically significant and clinically meaningful improvement in median PFS in patients with HER2-positive metastatic breast cancer. Improvement in PFS with pertuzumab was consistent across subgroups, and the immature ORR and OS results are consistent with the trend seen in PFS. The incidence of some adverse events increased with the addition of pertuzumab relative to the control; however, most adverse events were grade 1 or 2 and were manageable. Cardiac adverse events were not increased. The authors concluded that the new combination regimen presented in this trial may change clinical

Discordance Between Central and Local Laboratory HER2 Testing From a Large HER2-Negative Population in VIRGO, a Metastatic Breast Cancer Registry

Accurate HER2 testing—and particularly a low rate of false negatives—is critical for delivering the correct therapies to patients with HER2-positive breast cancer. To determine the discordance rate between local and central HER2 testing, tissue samples from patients with HER2-negative disease based on local testing were tested centrally, at a single laboratory, using the FDA-approved IHC HercepTest kit for protein expression and FISH PathVysion HER2 DNA probe kit for HER2 gene amplification. The lead investigator of this study was Vogel (Poster P1-07-02). Tissue samples were obtained from the VIRGO (An Observational Study of Treatment Patterns and Safety Outcomes for Metastatic or Locally Recurrent Breast Cancer) observational cohort study of 1,265 patients with HER2-negative metastatic breast cancer undergoing first-line treatment with endocrine therapy. Results from central testing were compared with the original results obtained from local testing. Of 489 unique patient samples, 478 were confirmed as HER2-negative by central testing. The remaining 21 (4.2%) samples tested HER2-positive (95% CI, 2.6–6.0%). Of the 21 samples deemed HER2-positive via central testing, 17 had been locally tested by only 1 methodology, and 9 samples tested positive using the methodology that had not been performed locally. Characteristics of patients with tumors that tested HER2-positive by central testing were consistent with those of the general HER2-positive population, and included younger age, tumors negative for expression of the estrogen and/or progesterone receptors, and shorter disease-free interval. Based on the testing discordance rate of 4.2%, it is estimated that 7,744 patients in the United States would test HER2-negative by central testing but HER2-positive by central testing with both methodologies. Extrapolated to the global population of breast cancer patients as estimated by the World Health Organization, the data imply that 46,487 patients could be affected annually by false negative results from HER2 testing. Given the significant clinical benefits derived from HER2-targeted therapies, the accurate identification of women with HER2-positive disease is critical. The results support the importance of testing for HER2 status using both FDA-approved tests for every tumor.

practice for first-line treatment of patients with metastatic breast cancer.

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Neoadjuvant Pertuzumab and Trastuzumab Concurrent or Sequential With an Anthracycline-Containing or Concurrent With an Anthracycline-Free Standard Regimen: A Randomized Phase II Study (TRYPHAENA)

The TRYPHAENA trial is a randomized, multicenter, international open-label phase II study to investigate neoadjuvant pertuzumab and trastuzumab in combination with an anthracycline-containing or an anthracycline-free standard chemotherapy regimen in patients with HER2-positive early breast cancer.¹ Trastuzumab and anthracyclines are important agents for treating HER2-positive breast cancer, but the combination has been associated with an increased risk of cardiotoxicity. The phase III Breast Cancer International Research Group (BCIRG) 006 study demonstrated the comparable efficacy and reduced toxicity of trastuzumab in combination with carboplatin and docetaxel relative to trastuzumab plus anthracycline.² As shown in the phase II NeoSphere study, the combination of trastuzumab, pertuzumab, and docetaxel yielded improved results over trastuzumab plus docetaxel while maintaining a manageable safety profile.³ In light of these findings, the TRYPHAENA trial was designed to assess the tolerability of neoadjuvant therapy consisting of pertuzumab plus trastuzumab plus either anthracycline/taxane-based or carboplatin/taxane-based chemotherapy in patients with HER2-positive early breast cancer. The study randomized 225 patients with centrally confirmed, HER2-positive, early breast cancer into 3 treatment arms (Table 1). Schneeweiss and associates presented results of the trial. The primary endpoint was cardiac safety defined as a symptomatic left ventricular systolic dysfunction (LVSD) or LVEF decline of at least 10% and below 50%. Secondary endpoints included toxicity; pathologic complete response (pCR) rate, defined

as the absence of invasive tumors in the breast at surgery; clinical response rate; and rate of breast-conserving surgery. In situ lesions were allowed, and node status did not impact the definition of pCR. The study was not powered for formal comparison between the 2 arms. Key eligibility criteria were centrally-confirmed HER2-positive disease; locally advanced or inflammatory early stage breast cancer with a primary tumor of at least 2 centimeters in diameter; baseline LVEF of at least 55%; and Eastern Cooperative Oncology Group performance status of 1. No previous anticancer therapy for malignancy was allowed, and adequate bone marrow and liver function were required.

The baseline characteristics were well-balanced across the treatment arms in the safety population of 223 patients. Median age was 45 to 50 years. Approximately half of the patients had

hormone receptor–negative breast cancer. Approximately two-thirds had inoperable disease at study entry, and 5–7% had inflammatory breast cancer. More than 90% of patients had HER2-positive disease based on IHC and FISH analysis.

Two patients in arm 2 (2.7%) experienced a symptomatic LVSD compared to no patients in the other 2 arms. Four, 3, and 2 patients experienced an LVSD in arm 1 (72 patients), arm 2 (75 patients), and arm 3 (76 patients), respectively. An LVEF decline between 10–50% occurred in 3, 4, and 3 patients in arms 1, 2, and 3, respectively. During the neoadjuvant treatment phase, prior to surgery, LVEF declined by approximately 2–6 percentage points and then returned to baseline. There was no significant difference in the change in mean LVEF across or between the treatment arms.

Table 1. Treatment Arms in the TRYPHAENA Trial*

Arm	Regimen	Dosages
1. Concurrent	3 cycles of FEC and concurrent trastuzumab/pertuzumab, followed by 3 cycles of docetaxel plus trastuzumab/pertuzumab	FEC: 5-fluorouracil (500 mg/m ²), epirubicin (100 mg/m ²), cyclophosphamide (600 mg/m ²) Carboplatin: AUC 6
2. Sequential	3 cycles of FEC followed by 3 cycles of docetaxel plus trastuzumab/pertuzumab	Pertuzumab: 840 mg loading; 420 mg maintenance Trastuzumab: 8 mg/kg loading; 6 mg/kg maintenance
3. Anthracycline-free	6 cycles of docetaxel plus carboplatin plus pertuzumab and trastuzumab	Docetaxel: 75 mg/m ² . In arms 1 and 2, dose escalation to 100 mg/m ² was allowed if tolerated

*All treatment was administered every 3 weeks. After adjuvant therapy, patients underwent surgical tumor removal followed by maintenance trastuzumab every 3 weeks to yield a total trastuzumab treatment of 23 weeks for each treatment arm.

AUC=area under the curve.

Data from Schneeweiss A. Paper presented at the 2011 San Antonio Breast Cancer Symposium; December 6-10, 2011; San Antonio, TX. Abstract S5-6.

However, at the time of the presentation, only 16% of all patients had completed the adjuvant treatment period.

The most common grade 3 or higher adverse events across all 3 treatment arms were neutropenia, febrile neutropenia, leukopenia, and diarrhea. In arms 1, 2, and 3, febrile neutropenia occurred in 18%, 9%, and 17% of patients, respectively, and diarrhea occurred in 4%, 5%, and 12% of patients, respectively. Compared to arms 1 and 2, arm 3 had more patients with diarrhea of grade 3 or higher, anemia, thrombocytopenia, vomiting, fatigue, and other adverse events.

The study yielded pCR rates of 62%, 57%, and 66%, respectively, in arms 1, 2, and 3, with pCR defined as no invasive tumors in the breast. Using a more conservative definition of pCR, which allows no invasive or noninvasive tumorous tissues in the breast and axilla, the pCR rates were 51%, 45%, and 52%,

respectively, in arms 1, 2, and 3. Patients with hormone receptor–negative disease experienced pCR rates of nearly 80% in arm 1 and 84% in arm 3. Patients with hormone receptor–positive disease also achieved pCR rates of 46–50%.

The objective response rates in arms 1, 2, and 3 were 92%, 95%, and 90%, respectively, with complete response rates of 51%, 28%, and 40.3%, respectively. Rates of breast-conserving surgery were available for arms 1, 2, and 3 in the 46, 36, and 37 patients for whom mastectomy was planned. Breast-conserving surgery was achieved in 22%, 17%, and 27% of patients in arms 1, 2, and 3, respectively.

In summary, the TRYPHAENA trial showed a low incidence of symptomatic and asymptomatic LVSD across all treatment arms. Cardiotoxicity was similar with concurrent administration of pertuzumab, trastuzumab, and epirubicin and for sequential administration

of the anthracycline-free regimen. The most frequent grade 3 or higher adverse events in all 3 arms were neutropenia, febrile neutropenia, leukopenia, and diarrhea. The combination of pertuzumab plus trastuzumab in the neoadjuvant setting achieved pCR rates ranging from 57–66% in combination with various chemotherapy regimens.

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Neoadjuvant Pertuzumab (P) and Trastuzumab (H): Biomarker Analyses of a 4-Arm Randomized Phase II Study (NeoSphere) in Patients (Pts) With HER2-Positive Breast Cancer (BC)

The phase II NeoSphere (Neoadjuvant Study of Pertuzumab and Herceptin in an Early Regimen Evaluation) trial was designed to examine the effect of adding the antibody pertuzumab to the combination of trastuzumab and docetaxel in patients with HER2-positive breast cancer. The study randomly assigned patients to 1 of 4 different treatments (Table 2). In results reported elsewhere, the trial showed that, compared to trastuzumab and docetaxel (TH) alone, TH plus pertuzumab (THP) induced a significantly higher rate of pCR (45.8% vs 29.0%; $P=.0141$), without a substantial increase in toxicity.¹ Additionally, pertuzumab plus trastuzumab (HP) in the absence of chemotherapy yielded pCRs in 17% of patients and showed a favorable safety profile.

Gianni and coworkers presented the results of biomarker analyses of tumor samples obtained from this trial.² Biomarker analyses were performed for the overall population. The group performed IHC, quantitative reverse transcriptase polymerase chain reaction (RT-PCR), FISH, enzyme-linked immunosorbent assay, and mutational analyses on specific target genes that are part of the HER2 signaling pathway. Especially in the last 5–7 years, interest has increased in the identification of actors in this pathway that increase or decrease the sensitivity to HER2-directed therapies. The number of samples ranged from 273–416. The cutoff for analyses of correlation with treatment and sensitivity was defined as the median for each biomarker, with the exception of c-Myc (ratio ≥ 2.0) and

PIK3CA status (wild type vs mutant). Of these analyses, only the HER2 membrane H-score was associated with a different probability of outcome, which was observed for the addition of pertuzumab to the TH regimen. However, the result was not clinically meaningful because of clustering within a small dynamic range. Phosphoinositide 3-kinase (PI3K) is an intracellular signaling molecule that interacts directly with HER2 and has been implicated in varying sensitivity to treatment. The mutational status of PIK3CA was initially assessed using a traditional assay that identified 8 mutations at 4 hotspots in exons 7, 9, and 20 of PIK3CA. By using a new method for examining material extracted from IHC-stained slides, the available sample size was increased to 329 cases. No

Table 2. Treatment Arms in the NeoSphere Trial

Arm	Number of Patients	Regimen
1	107	Trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg maintenance) plus docetaxel (75 mg/m ² , escalating, if tolerated, to 100 mg/m ²)
2	107	Trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg maintenance) and docetaxel (75 mg/m ² , escalating, if tolerated, to 100 mg/m ²) plus pertuzumab (840 mg loading dose, followed by 420 mg maintenance)
3	107	Pertuzumab (840 mg loading dose, followed by 420 mg maintenance) plus trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg maintenance)
4	96	Docetaxel (75 mg/m ² , escalating, if tolerated, to 100 mg/m ²) plus pertuzumab (840 mg loading dose, followed by 420 mg maintenance)

Data from Gianni L. Paper presented at the 2011 San Antonio Breast Cancer Symposium; December 6-10, 2011; San Antonio, TX. Abstract S5-1.

association between mutational status and non-pCR versus pCR was detected for samples from patients in any of the 4 treatment arms. However, a pooled comparison of pCR/non-pCR showed that patients with a mutation in exon 9 had a ratio of 2 pCR/28 non-pCR, or a 7.1% chance of achieving a pCR. Thus, the exon 9 mutation may be associated with resistance to therapy. In comparison, the pooled analysis of samples with exon 20 mutations showed a ratio of 19 pCR/66 non-pCR, or a 28.7% chance of pCR.

The estrogen and the HER2 receptor pathways are known to engage in cross-talk whose importance was reflected in the clear increase in disease eradication for patients with hormone receptor–negative disease. The difference in response was especially striking in the patients who received THP treatment, with a 26% pCR rate in patients with ER- or PR-positive tumors versus 63.2% for those with hormone receptor–negative tumors. The discrepancy is not mediated by chemotherapy, as shown by the responses in patients treated with the antibody combination alone (5.9% for ER- or PR-positive vs 29.1% for patients with hormone receptor–negative tumors).

Analysis of PIK3CA mutation relative to ER status showed that approximately 32% of all patients had a PIK3CA mutation, and this percentage was maintained when the tissue was pooled into ER-positive or ER-negative status. However, an imbalance in PIK3CA mutations between the 2 groups could not be ruled out due to small sample size. Nonetheless, 10 out

of 16 biomarkers examined showed a distinct increase in expression for tissue that was ER-positive versus ER-negative (false discovery rate <0.05), including membrane IGF-1R by histology, HER3 by RT-PCR, membrane HER3 by histology, cytoplasmic PTEN by histology, epidermal growth factor receptor by RT-PCR, and serum amphiregulin.

Because the NeoSphere trial was not designed with biomarker analysis as the primary endpoint, the analysis of differential marker expression and ER status did not yield information that could be clinically exploited. An examination of pCR rates in ER-negative samples suggested that exposure to TP without chemotherapy in patients with high levels of HER2 mRNA yielded a higher rate of pCR than in patients with a low level of HER2 mRNA ($P=.02$). However, only 54 samples total were available for this analysis. This trend was not observed with the 48 ER-positive patients. Similarly, a higher rate of pCR was observed for THP versus TH for patients with low IGF1R expression (69% vs 33%, respectively; $P=.004$). This trend was not observed for patients with high IGF1R expression ($P=.95$). Again, however, caution in interpreting the results is needed given the small sample sizes (65 samples for low IGF1R expression and 33 samples for high IGF1R expression).

Resistance to trastuzumab has been proposed to arise in many cases from the expression of p95, a truncated form of HER2. Truncated forms of HER2 may arise through the shedding of HER2,

induced by metalloproteinases, or by alternative translation initiation. Gianni and colleagues developed an automated assay for determining the ratio of extracellular domain to intracellular domain, which in turn reflects the relative amount of intact versus truncated HER2 protein in the tumor sample. An extracellular domain/intracellular domain of less than 1 indicates the presence of truncated HER2. Examination of 149 samples based on treatment received showed no association between the presence of truncated HER2 and response to treatment.

In summary, HER2 expression was associated with sensitivity to pertuzumab, PIK3CA mutations in exon 9 were linked to lack of sensitivity to antibodies against HER2, and hormone receptor status was shown to correlate with response to anti-HER2 antibody therapy. Results from the presented analyses did not provide any clinically useful assays to improve patient or regimen selection as a supplement or alternative to conventional assessment of HER2 by IHC or FISH.

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A Phase 2, Randomized, Open-Label, Study of Neratinib (HKI-272) vs Lapatinib Plus Capecitabine for 2nd/3rd-Line Treatment of HER2+ Locally Advanced or Metastatic Breast Cancer

Martin and associates presented the results from a phase II, open-label study of neratinib.¹ Neratinib is an orally active, irreversible pan-ErbB receptor tyrosine kinase inhibitor, targeted against HER2, HER1, and HER4. In a prior study of neratinib in patients with advanced or metastatic HER2-positive breast cancer, patients previously treated with trastuzumab showed an ORR of 24% and a median PFS of 22.3 weeks with neratinib monotherapy.² Patients who were trastuzumab-naïve showed an ORR of 56% and a median PFS of 39.6 weeks. The most common adverse event was diarrhea.

The current study was originally designed as a phase III trial involving approximately 1,000 patients and powered to assess the superiority of neratinib over the combination of lapatinib plus capecitabine (LC). Before any planned interim analysis, the study design was amended to a randomized phase II study of 230 patients to assess the noninferiority of neratinib monotherapy versus LC, and to attain a greater understanding of the efficacy and tolerability of neratinib monotherapy compared to an established combination therapy. In the phase II design, HER2-positive patients with locally advanced or metastatic breast cancer were randomized to neratinib 240 mg/day (117 patients) or the standard combination of lapatinib 1,050 mg/day plus capecitabine 2,000 mg/m² on days 1–14 of a 21-day cycle (116 patients). The trial was designed based on a 1-sided log-rank test with $\alpha=0.1$ and 85% power.

Key eligibility criteria included women with HER2-positive, locally

advanced or metastatic breast cancer not amenable to curative therapy; disease progression on or following no more than 2 trastuzumab-based regimens; prior treatment with a taxane regimen; prior anthracycline treatments at or below the maximum cumulative dose of 400 mg/m² for doxorubicin, 800 mg/m² for epirubicin, or the equivalent dose for other anthracycline derivatives; and measurable disease, including at least 1 measurable lesion, as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. The primary endpoint of the trial was PFS from the day of randomization. Secondary endpoints were ORR, clinical benefit rate (ORR plus rate of stable disease at or after 24 weeks), safety, and OS. Most baseline characteristics were well-balanced between the 2 arms. More patients in the LC arm had received prior trastuzumab in the neoadjuvant or adjuvant setting (32% vs 20%), and more patients in the neratinib arm had received trastuzumab in the metastatic setting (79% vs 68%).

The median duration of treatment was 127.5 days (range, 1–715 days) with neratinib (n=116) and 203 days (range, 12–622) with LC (n=115). Median dose intensity was 100% (range, 38–100%) with neratinib, 95% (range, 38–100%) with lapatinib, and 84% (range, 26–111%) with capecitabine. Dose reductions occurred in 23% of neratinib recipients, 28% of lapatinib recipients, and 70% of capecitabine recipients.

In the neratinib arm, diarrhea was the most common toxicity and was documented in 85% of patients.

The predominant toxicities reported in the combination arm were diarrhea (68%) and hand and foot syndrome (65%). The most common grade 3/4 toxicities were diarrhea (28%) in the neratinib arm and diarrhea (10%) and hand and foot syndrome (14%) in the LC arm. The median time to onset of diarrhea was 3 days with neratinib versus 7 days with LC; however, the median duration was only 3 days in each arm. Moreover, the diarrhea was manageable in most patients, with treatment discontinuation due to this event occurring in only 2% of patients treated with neratinib and 4% of patients treated with LC. Dose reductions and dose delays were more frequent in the combination arm (53% vs 74%, respectively) than in the neratinib arm (19% vs 32%, respectively). No deaths due to toxicity were reported for either arm.

Median PFS was higher with the combination treatment versus neratinib monotherapy, although the difference was not significant (6.8 months vs 4.5 months; $P=.231$). OS did not differ significantly between the 2 arms (19.7 months with neratinib vs 23.6 months with LC; $P=.280$). The non-inferiority analysis yielded an HR of 1.19 for PFS with neratinib versus LC in the intent-to-treat population. This HR crossed the noninferiority margin of 1.15, and thus the trial failed to demonstrate noninferiority of neratinib monotherapy compared to LC. The ORR was higher in the combination therapy arm (40%) compared to the neratinib arm (29%). The clinical benefit was also greater in the LC arm (63%) compared to the neratinib arm (44%).

Neratinib monotherapy did not achieve noninferiority for PFS relative to LC in this trial. However, given the heavily pretreated population, neratinib monotherapy showed robust antitumor activity, yielding an ORR of 29% and a clinical benefit rate of 44%. Neratinib monotherapy was associated with numerically fewer dose reductions, dose delays, or discontinuations compared to the standard treatment of LC. Diarrhea was the most frequently reported adverse event, but it was transient and manageable. The authors concluded that continued development of neratinib as monotherapy or in combination with other agents for the treatment of recurrent, HER2-positive breast cancer is warranted based on the results of this clinical trial. A phase III trial comparing lapatinib plus capecitabine versus neratinib plus capecitabine is being considered.

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Entinostat, a Novel Histone Deacetylase Inhibitor, Added to Exemestane Improves PFS in Advanced Breast Cancer in a Randomized, Phase II, Double-Blind Study

Entinostat is a class I-selective histone deacetylase inhibitor that counteracts aromatase inhibitor resistance. Yardley presented results from a double-blind phase II study of postmenopausal women with ER-positive, advanced breast cancer who were randomized 1:1 to exemestane 25 mg/day plus weekly entinostat 5 mg or placebo (Abstract PD 01-04). Patients had progressed on a nonsteroidal aromatase inhibitor and had received no more than 1 prior chemotherapy. Patients with aromatase inhibitor-sensitive disease had experienced a PR, CR, or SD for at least 6 months in the metastatic setting or had completed therapy and remained disease-free for at least 12 months after adjuvant nonsteroidal aromatase inhibitor therapy. All other patients were considered aromatase inhibitor-resistant. PFS was the primary endpoint. Statistical significance was defined prospectively as $P < .10$. Sixty-four women were randomized into the entinostat combination arm and 66 into the placebo plus exemestane control arm. At baseline, 82% of the patients had measurable disease, of whom 60% had visceral involvement. Forty-two percent had received 1 prior line of hormonal therapy, and the remaining patients had received more than 1 prior line of hormonal therapy. In the intent-to-treat population, median PFS increased to 4.28 months in the entinostat combination arm versus 2.27 months in the control arm (HR, 0.73; 95% CI, 0.49–1.09; $P = .06$). Predefined patient subsets consistently showed improved PFS with the combination treatment, although the analyses were not powered to demonstrate statistical significance. Even in the subset of patients with predefined aromatase inhibitor-resistant disease, PFS improved numerically relative to placebo, with a median PFS of 3.72 months versus 1.78 months, respectively (HR, 0.61; 95% CI, 0.30–1.25). Early evaluation of OS at 18 months' follow-up also suggests improvement with the combination treatment, with median OS rates of 26.94 months versus 20.33 months (HR, 0.56; 95% CI, 0.31–1.02). The combination of entinostat plus exemestane was well tolerated. The most frequent AEs were fatigue, gastrointestinal disturbances, and hematologic abnormalities. AEs with an incidence of at least 20% greater in the combination arm were fatigue (46% vs 26%) and uncomplicated neutropenia (25% vs 0%). The rates of serious AEs were similar for both arms. These results suggest that the addition of entinostat to aromatase inhibitor therapy can extend PFS, thus delaying the need for subsequent treatments.

A Phase III Randomized Trial of Anastrozole Versus Anastrozole and Fulvestrant as First-Line Therapy for Postmenopausal Women With Metastatic Breast Cancer: SWOG S0226

Because anastrozole lowers estrogen levels and fulvestrant decreases expression of the estrogen receptor, combining these 2 agents could yield additive activity in postmenopausal breast cancer. Fulvestrant showed high activity in a low-estrogen in vivo model of human breast cancer, and the combination of anastrozole and fulvestrant decreased the expression of several resistant proteins in an in vivo model.^{1,2} The phase III S0226 trial was undertaken to compare the efficacy and tolerability of anastrozole plus fulvestrant versus anastrozole alone.³ Mehta and colleagues presented results of this trial. Eligible patients were postmenopausal women with metastatic breast cancer that was either measurable or nonmeasurable and was hormone receptor–positive. Eligible patients had not received prior chemotherapy, hormonal therapy, or immunotherapy for their metastatic disease. Prior adjuvant tamoxifen was allowed, and patients were stratified based on this factor. Therapy with an adjuvant aromatase inhibitor, neo-adjuvant chemotherapy, or adjuvant chemotherapy was allowed if completed at least 12 months prior to the study start. Neither chemotherapy nor another hormone therapy were allowed during study treatment.

Patients in Arm 1 received anastrozole 1 mg/day until progression, and crossover to fulvestrant monotherapy was strongly encouraged after progression. Patients in Arm 2 received anastrozole 1 mg/day plus fulvestrant until progression, with fulvestrant 500 mg administered on day 1, and

fulvestrant 250 mg administered on days 14 and 28, followed thereafter by maintenance fulvestrant 250 mg on day 28 of every 28-day cycle.

The primary endpoint was PFS. The trial was designed with a 90% power to detect an increase in median PFS from 10 months to 13 months with a 2-sided alpha of 0.05. Two interim analyses of the primary endpoint were planned at 50% and 75% of the events. Subset analyses were not planned. OS was a secondary endpoint.

A total of 707 patients were randomized, and the final analysis included 345 patients in the anastrozole monotherapy arm and 349 patients in the anastrozole plus fulvestrant arm. Most patient characteristics were well-balanced between the 2 arms. Median age was 65 years; 40% of patients had received prior adjuvant tamoxifen; 30% of patients in the monotherapy arm and 37% of patients in the combination arm had received prior adjuvant chemotherapy. In both arms, disease was measurable in 54% of patients; in 22% of patients, bone was the only site of metastases. De novo metastatic disease was noted in 42% of patients in arm 1 and 36% of patients in arm 2. In arm 1 versus arm 2, more than 10 years had elapsed since the previous diagnosis in 26% and 10% of patients, respectively. Slightly more patients had HER2-positive disease in arm 2 versus arm 1 (10.4% vs 8.5%, respectively).

After February 15, 2011, patients in either arm were allowed to cross over to 500 mg fulvestrant monotherapy after progression. Of the 345 patients

on anastrozole only, 143 crossed over to fulvestrant, including 5 patients who opted for the 500 mg dosing. Nine patients out of 349 in the combination arm received the fulvestrant 500 mg dosing after progression.

Median PFS was 13.5 months for arm 1 and 15 months for arm 2 (HR, 0.80; 95% CI, 0.68–0.94; $P=0.0070$). Analysis of patients with prior adjuvant tamoxifen therapy showed no significant difference in PFS for patients treated in the current trial with anastrozole alone (141 patients) versus anastrozole plus fulvestrant (139 patients; 14.1 months vs 13.5 months, respectively; HR, 0.89; 95% CI, 0.69–1.15; $P=.37$). In contrast, a benefit was seen for patients who had not received prior adjuvant tamoxifen: PFS was 12.6 months in arm 1 (208 patients) and 17 months in arm 2 (206 patients; HR, 0.74; 95% CI, 0.59–0.92; $P=.0055$). Median OS showed a strong trend toward improved survival for the combination treatment (41.3 months in arm 1 vs 47.7 months in arm 2; HR, 0.81; 95% CI, 0.65–1.00; $P=.049$). No OS benefit was observed for patients who had received prior adjuvant tamoxifen treatment. Median OS was 44.5 months in arm 1 ($n=141$) versus 49.6 months in arm 2 ($n=139$; HR, 0.91; 95% CI, 0.65–1.28; $P=.59$). In patients with no prior adjuvant tamoxifen treatment, median OS was 39.7 months in the anastrozole-only group (208 patients) versus 47.7 months in the combination therapy group (206 patients; HR, 0.74; 95% CI, 0.56–0.98; $P=.0362$).

Results from the unplanned analyses based on prior tamoxifen

treatment suggest a possible benefit in only the tamoxifen-naïve patients. However, prior tamoxifen treatment was confounded with the time between adjuvant and metastatic diagnoses. Additional unplanned analyses based on age, HER2 status, visceral or nonvisceral disease, bone metastasis only, disease measurability, years since diagnosis, and exposure to prior chemotherapy or tamoxifen suggest that most patients benefited from the combination treatment.

In the combination treatment arm, 2 deaths were attributed to pulmonary embolism and 1 death to cerebrovascular ischemia. However, the investigators did not attribute the deaths directly to the effects of the combination therapy. Two other patients in the same arm had grade 4 toxicities: neutropenia and lymphopenia occurred in 1 patient, and pulmonary embolism occurred in the other. Four patients on anastrozole monotherapy had grade 4 toxicities that included thrombosis/embolism, arthralgia, thrombocytopenia, and dyspnea. Grade 3 toxicities were nominally higher in the combination arm (13% vs 11%) and included musculoskeletal pain, fatigue, hot flashes, mood alterations, and gastrointestinal symptoms with a frequency of 1–4%. Adverse events did not differ significantly between the 2 arms. Treatment was stopped early in few patients (4 patients in Arm 1 and 11 patients in Arm 2).

A separate phase III study by Bergh and colleagues also investigated anastrozole treatment with or without fulvestrant in breast cancer patients.⁴ However, the study failed to find a significant difference in OS between the 2 treatment arms. The success of the current study may be explained by the fact that, in contrast to the study by Bergh and colleagues, patients in the

Patient-Reported Outcomes From a Randomized Phase II Study (TDM4450g/BO21976) of Trastuzumab Emtansine vs Trastuzumab Plus Docetaxel in Previously Untreated Human Epidermal Growth Factor Receptor 2–Positive Metastatic Breast Cancer

T-DM1, or trastuzumab emtansine, comprises the trastuzumab antibody plus approximately 3 covalently bound copies of the microtubule inhibitor, DM1, per antibody. A randomized, multicenter, open-label, phase II study (TDM4450g/BO21976) was conducted to assess the efficacy and safety of T-DM1 (3.6 mg/kg) versus trastuzumab (H); 8 mg/kg followed by 6 mg/kg) plus docetaxel (T); 75 or 100 mg/m²) in treatment-naïve patients with HER2-positive metastatic breast cancer. The lead investigator was Bianchi (Poster PI-12-02). Treatment was administered every 3 weeks. Out of 137 patients total, the 67 patients in the T-DM1 arm experienced an improved median PFS (14.2 months vs 9.2 months; HR, 0.59; $P=.035$) and a significant reduction in AEs of grade 3 or higher (46% vs 89%). The trial also examined patient quality of life via the Functional Assessment of Cancer Therapy—Breast (FACT-B) Trial Outcome Index (TOI). Worsening of the FACT-B-TOI scores was significantly delayed in the 65 evaluable patients treated with T-DM1 compared to the 67 evaluable patients treated with HT, with median times to symptom progression of 7.5 months versus 3.5 months, respectively (HR, 0.58; $P=.022$). Five of 7 indicators of patient well-being were significantly better in patients treated with T-DM1, including “bothered by side effects” ($P<.001$), “feeling ill” ($P=.016$), “forced to spend time in bed” ($P=.015$), “lack of energy” ($P=.011$), and “trouble meeting needs of family” ($P=.025$). Scores for the indicators nausea and pain were numerically superior with T-DM1 but did not reach statistical significance.

monotherapy arm were not allowed to cross over to the combination treatment arm; instead, they were allowed to receive fulvestrant monotherapy after disease progression. In addition, the patient population in the current study may have had disease with greater endocrine sensitivity.

In summary, first-line combination of anastrozole and fulvestrant improved PFS and OS in postmenopausal women with HR-positive breast cancer. Although toxicity was comparable for the monotherapy and combination treatments, grade 5 toxicity was seen only with the combination.

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Trials of Bisphosphonates in Breast Cancer

Bisphosphonates are of interest for their potential in protecting against cancer-treatment-induced bone loss, preventing bone metastases, reducing pain, and improving disease-free survival (DFS). By inhibiting osteoclast function and bone turnover, bisphosphonates may inhibit the growth of bone metastases. Four research groups reported results from trials of bisphosphonates combined with various chemotherapy regimens.

ZO-FAST: 5-Year Follow-Up

De Boer and colleagues reported 5-year follow-up results from the ZO-FAST (Zometa-Femara Adjuvant Synergy) trial, which compared adjuvant letrozole and zoledronic acid in postmenopausal women with hormone receptor-positive early breast cancer.¹ Earlier results from the same trial showed that the addition of zoledronic acid to adjuvant therapy significantly improved bone mineral density (BMD) and prolonged DFS compared to delayed treatment with zoledronic acid.²

The ZO-FAST trial enrolled 1,065 postmenopausal women with hormone receptor-positive early breast cancer and a BMD T-score of at least -2.0. The patients received letrozole (2.5 mg/day for 5 years), and were randomized to 5 years of treatment with either immediate or delayed zoledronic acid (4 mg every 6 months). Delayed zoledronic acid was administered if the patient had a T-score of 2.0 or less or experienced a fracture (clinical or asymptomatic) by 36 months. The primary endpoint was BMD at 12 months. Secondary endpoints included BMD at 36 months and 60 months, disease recurrence, fracture incidence, and safety.

Baseline characteristics were well-balanced between the 2 arms. After 60 months of follow-up, patients who had received immediate zoledronic

Results of a Randomized, Double-Blind, Multicenter, Placebo-Controlled Study of Adjuvant Lapatinib in Women With Early-Stage ErbB2-Overexpressing Breast Cancer

The international, randomized, double-blind, placebo-controlled, phase III TEACH (Tykerb Evaluation After Chemotherapy) trial is examining lapatinib in patients with HER2-positive, stage I-IIIc breast cancer previously treated with neoadjuvant or adjuvant chemotherapy only. Results were presented by Goss (Abstract S4-7). The trial objective is to determine whether 1 year of adjuvant lapatinib therapy can improve disease-free survival in patients with HER2-positive disease who do not receive adjuvant trastuzumab. Patients were allowed to enroll in the trial at any time following primary diagnosis. The study randomized 3,161 patients in a 1:1 ratio to receive either oral lapatinib 1,500 mg (1,571 patients) or placebo (1,576 patients) daily for 1 year. Stratification factors included time from diagnosis, nodal status, and hormone receptor expression status. The primary endpoint was disease-free survival (defined as absence of recurrence, second primary cancer, or death before recurrence). Secondary endpoints included OS, recurrence-free survival, central nervous system recurrence rate, toxicities, and quality of life. The median time from diagnosis to randomization was 2.7 years. After a median follow-up of 4 years, the difference in disease-free survival for lapatinib versus placebo did not reach statistical significance (HR, 0.83; 95% CI, 0.70-1.00; $P=.053$). OS did not differ significantly between the 2 arms (HR, 0.99). Preplanned subgroup analysis of 1,288 patients revealed a significant benefit with lapatinib for hormone receptor-negative disease (HR, 0.68; 95% CI, 0.52-0.89; $P=.006$) and for the 647 patients randomized within 1 year of diagnosis (HR, 0.70; 95% CI, 0.50-0.99). For FISH-positive patients, symptomatic central nervous system recurrences were delayed and less frequent in the lapatinib arm than in the placebo arm. An unplanned analysis of the subgroup of 2,490 patients with centrally confirmed HER2 expression via FISH yielded a DFS benefit with lapatinib treatment. AEs were more common in the lapatinib arm (92% vs 76%), including grade 3/4 events (23% vs 8%). No evidence of cardiac toxicity was observed in the lapatinib arm, and there were no treatment-related deaths.

acid showed 10% greater lumbar spine BMD compared to the delayed arm ($P<.0001$) and 5.8% greater total hip BMD ($P<.001$). The immediate zoledronic acid arm also showed a significantly reduced risk of a DFS event by 34% compared to the delayed arm in the intent-to-treat population of 1,065 patients (HR, 0.66; $P=.0375$). OS was similar between the 2 arms ($P=.196$).

Exploratory analyses of 670

women who were either postmenopausal for at least 5 years or were older than 60 years of age at study entry showed an improved DFS (HR, 0.63; 95% CI, 0.39-1.01; $P=.052$) and OS (HR, 0.050; 95% CI, 0.27-0.92; $P=.022$) for treatment with immediate versus delayed zoledronic acid. In the delayed treatment arm, a reduced risk of DFS events was observed for those who initiated zoledronic acid com-

Table 3. Confirmed Cases of ONJ in Clinical Trials of Zoledronic Acid

Trial Name	Follow-Up	Number of Confirmed Cases of ONJ	Number of Study Participants	Percent of Confirmed ONJ Cases
ZO-FAST ¹	5 years	3	1,065	0.56
Z-FAST ⁸	5 years	0	601	0
E-ZO-FAST ⁹	3 years	1	527	0.19
ABCSG-12 ¹⁰	>5 years	0	1,803	0
AZURE ¹¹	5 years	17	3,360	1.1

ABCSG-12=Austrian Breast and Colorectal Cancer Study Group trial 12; AZURE=Adjuvant Zoledronic Acid to Reduce Recurrence; E-ZO-FAST=Zometa-Femara Adjuvant Synergy Trial; ONJ=osteonecrosis of the jaw; Z-FAST=Zometa-Femara Adjuvant Synergy Trial; ZO-FAST=Zometa-Femara Adjuvant Synergy Trial.

pared to those who did not ($P=.033$), whereas an increased risk was observed for those who were at least 65 years old ($P=.024$) and had a tumor stage status of T2 or greater ($P=.042$).

Adverse events were consistent with the known safety profiles of the drugs. During 5 years of treatment, 3 confirmed cases of osteonecrosis of the jaw were reported out of 1,065 patients total (0.56%). Other trials of zoledronic acid reported up to 1.1% of confirmed cases of osteonecrosis of the jaw (Table 3).

ABCSG-12: 84-Month Follow-Up

Gnant and coworkers presented the latest results of the ABCSG-12 (Austrian Breast and Colorectal Cancer Study Group trial 12) trial, showing an OS benefit.³ Results from preplanned subset analyses were also presented. The trial enrolled 1,803 premenopausal women with hormone receptor-positive, early stage breast cancer. Patients were randomized equally into 4 arms to receive goserelin (3.6 mg every 28 days) and tamoxifen (20 mg/day) or anastrozole (1 mg/day), either with or without zoledronic acid (4 mg every 6 months), for 3 years. The primary endpoints were DFS and OS.

At a median follow-up of 84 months, a 28% reduction in the risk of a DFS event (the primary endpoint) was observed for patients in the zoledronic acid combined therapy arm (HR, 0.72; 95% CI, 0.56–0.94; $P=.014$). This arm

also had a 41% reduction in the risk of death (HR, 0.59; $P=.027$). In the 1,390 patients older than 40 years, zoledronic acid-based therapy significantly reduced the risk of a DFS event by 34% (HR, 0.66; $P=.014$) and decreased the risk of death by 49% (HR, 0.51; $P=.020$). No significant benefit was seen in patients ages 40 years or younger.⁴ Subset analyses showed a benefit with zoledronic acid in patients with T1 tumor status ($P=.038$) and node-positive disease ($P=.037$). All patients progressed to the follow-up phase, and there were no reported cases of osteonecrosis of the jaw or renal failure. The results suggest that sufficient suppression of dormant micrometastases requires both estrogen deprivation and reduction of growth factors derived from bone turnover in the bone marrow microenvironment.

B-34: 8-Year Follow-Up

The National Surgical Adjuvant Breast and Bowel Project B-34 study is a randomized, double-blind, placebo-controlled, phase III clinical trial in patients with stage I–III breast cancer.⁵ The trial randomized 3,323 patients 1:1 to receive either oral clodronate (1,600 mg/day) or placebo for 3 years. Patients were allowed to receive adjuvant chemotherapy, with or without tamoxifen, at the investigator's discretion. Patients were stratified by age, number of positive lymph nodes, and hormone receptor status. The primary endpoint was

DFS. Secondary endpoints included incidence of skeletal metastases, OS, relapse-free survival, incidence of non-skeletal metastases, and incidence of skeletal morbid events.

Paterson and associates presented results of the trial.⁵ After a median follow-up of 8.41 years for 3,311 patients, only 42% of patients had completed 3 years of treatment. No significant difference in DFS was discerned (HR, 0.91; 95% CI, 0.778–1.072; $P=.266$). However, for patients ages 50 years or older, a significant reduction was seen for the interval without bone metastasis (HR, 0.61; $P=.024$) and the interval without metastasis other than bone (HR, 0.63; $P=.015$).⁶ One case of osteonecrosis of the jaw was observed in the clodronate arm versus no cases with the placebo.

GAIN: 39-Month Follow-Up

The GAIN (German Adjuvant Intergroup Node Positive) study is a multicenter, controlled, nonblinded, randomized phase III trial that examined the administration of ibandronate after dose-dense chemotherapy.⁷ Möbus and colleagues presented results of the study, in which patients were first randomized to receive either ETC (epirubicin [E]: 150 mg/m², paclitaxel [T]: 225 mg/m², cyclophosphamide [C]: 2,500–2,000 mg/m², day 1, every 2 weeks for 3 cycles each) or EC-TX (E: 112.5 mg/m² plus C: 600 mg/m², day 1, every 2 weeks for 4 cycles followed by T: 67.5 mg/m² day 1, weekly for 10 weeks plus capecitabine [X]: 2,000 mg/m² days 1–14, every 3 weeks for 4 cycles). Patients were then randomized 2:1 to receive ibandronate (50 mg/day orally for 2 years or to undergo observation. Eligible patients were women ages 18–65 years with histologically confirmed lymph node-positive, unilateral or bilateral breast cancer. The primary objective was to compare the DFS for ETC versus EC-TX and for ibandronate versus observation. Secondary objectives included OS and safety.

The trial recruited 3,023 patients. An interim analysis showed that the futility boundary had been crossed for

the comparison of ibandronate versus observation. With a median follow-up of 39 months, the data showed no difference in either DFS or OS for treatment with or without the oral bisphosphonate (DFS: HR, 0.945; 95% CI, 0.768–1.16; $P=.59$; OS: HR, 1.04; 95% CI, 0.763–1.42; $P=.80$). Subgroup analyses likewise showed no significant difference between the treatments.

In summary, these 4 trials of bisphosphonates yielded inconsistent results. The appropriate application of bisphosphonates in treating patients with breast cancer remains to be clarified.

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Commentary

Charles L. Vogel, MD

Professor of Clinical Medicine
Sylvester Comprehensive Cancer Center at Deerfield
Miller School of Medicine, University of Miami
Miami, Florida and
Clinical Director
Cancer Research Network
Deerfield Beach, Florida

There were many interesting studies presented at the 2011 San Antonio Breast Cancer Symposium (SABCS). Several trials compared single-agent hormonal therapy to dual hormonal blockade, while others compared single-agent therapy to combined therapy with another, non-hormonal biologic. Other trials identified the false negative rate of HER2/neu testing, and examined whether bisphosphonates can improve progression-free survival (PFS). Trials presented at the meeting may also lead to the eventual approval of 2 new agents: pertuzumab and T-DM1.

The BOLERO-2 Trial

One of the most important studies presented at the 2011 SABCS was the BOLERO-2 trial.¹ Previous results were presented at the 2011 European Society for Medical Oncology (ESMO) meeting.² Patients were estrogen receptor–positive and HER2/neu negative. They were randomized after they progressed while receiving a non-steroidal aromatase inhibitor and then treated with exemestane as a single agent or exemestane plus everolimus (RAD-001). Two companion trials

in HER2-positive metastatic disease were BOLERO-1, a first-line trial of everolimus in combination with chemotherapy and trastuzumab,³ and BOLERO-3, a second- and third-line study of vinorelbine and trastuzumab with or without everolimus.⁴ However, results of neither trial are yet available.

In the BOLERO-2 trial, the primary endpoint of PFS was highly statistically significant in favor of the everolimus-exemestane combination (10.6 months) compared with 4.1 months in the placebo group, by independent central review.¹ The clinical

benefit rate, defined as the response rate plus prolonged stable disease for greater than 6 months, almost doubled with the addition of everolimus, increasing from 25.5% to 50.5%. The response rate itself was very low in both groups, and was virtually nonexistent in the exemestane group at 1.3%, compared with 12% in the everolimus group. There were toxicities associated with everolimus, including stomatitis, fatigue, and anemia, although most of these were only grade 1 or 2. Some patients developed hyperglycemia and liver function abnormalities, while most importantly, some developed a peculiar drug-related pneumonitis. The addition of everolimus to a drug like exemestane (as long as the toxicity profile is reasonable) may allow patients to avoid standard chemotherapy for a longer period of time, and this is a benefit that clinicians must consider when the drug becomes commercially available for breast cancer.

The CLEOPATRA Trial

A second major advance occurred in the CLEOPATRA trial, a first-line metastatic disease trial for HER2/neu-positive patients.^{5,6} Patients in the CLEOPATRA trial were randomized to receive standard chemotherapy with docetaxel plus trastuzumab or docetaxel plus trastuzumab with the addition of pertuzumab, which inhibits dimerization of HER2 and other members of the HER family, most preferentially HER3. Approximately 800 patients were enrolled in this trial, and PFS was a major endpoint. The results were impressive. The addition of pertuzumab increased PFS to 18.5 months versus 12.4 months with standard chemotherapy and trastuzumab. The response rate was also better, reaching 80.2% in the combined targeted approach versus 69.3%. Overall, this very important trial, combined with other important studies such as NeoSphere⁷ and TRYPHAENA⁸ (discussed below) will probably lead to approval for pertuzumab in patients who are HER2/neu-positive.

The NeoSphere Trial

In the NeoSphere trial, the addition of pertuzumab to a regimen of trastuzumab and docetaxel as neoadjuvant therapy was associated with a significantly higher rate of pathologic complete response compared to trastuzumab and docetaxel alone (45.8% vs 29.0%; $P=.0141$).⁷ Pertuzumab did not increase toxicity. In addition, a regimen of pertuzumab plus trastuzumab without docetaxel was associated with a pathologic complete response of 17%, with a favorable safety profile. At the SABCS, a biomarker analysis of the NeoSphere trial showed that HER2 expression was associated with sensitivity to pertuzumab, PIK3CA mutations in exon 9 were linked to lack of sensitivity to antibodies against HER2, and hormone receptor status was shown to correlate with response to anti-HER2 antibody therapy.⁹

The TRYPHAENA Trial

Pertuzumab was also studied in the neoadjuvant trial TRYPHAENA.⁸ In this trial, pertuzumab and trastuzumab were administered with or after a regimen that contained an anthracycline followed by single or dual HER2-targeted agents with docetaxel. A third comparator arm was docetaxel plus carboplatin with dual HER2-targeted blockade. All regimens in this trial did equally well in achieving a pathologic complete response. When defined as eradication of the disease in the lymph nodes as well as in the breast, the pathologic complete response was 45–52%, while the rate was 57–66% when defined as disappearance of the disease only in the breast. Previous studies have suggested that trastuzumab given with an anthracycline can increase cardiac toxicity. Congestive cardiac failure (CHF) was seen in only 2.7% of patients in the entire series. It occurred in the patients who received docetaxel and pertuzumab after epirubicin but not in patients who received concomitant epirubicin with

the targeted therapies nor in those not receiving epirubicin-based therapy. Aside from the rare occurrence of CHF noted above, a reduction in the left ventricular ejection fraction was not frequent, although the rate was highest in the patients who received 5-fluorouracil, epirubicin, and cyclophosphamide plus trastuzumab and pertuzumab, at 5.6%, and lowest in the patients who received docetaxel, carboplatin, trastuzumab, and pertuzumab, at 2.6%.

The CLEOPATRA, NeoSphere, and TRYPHAENA trials show that pertuzumab has very good potential to add to the effectiveness of trastuzumab in the management of patients with HER2/neu-positive breast cancer. These trials expand on our recently published review of dual HER-2 blockade.¹⁰ An ongoing adjuvant trial is investigating whether pertuzumab can improve curability.

The VIRGO Trial

Few studies have examined the false negative rate of HER2/neu testing. The immunohistochemistry scale is 0 to 1+, 2+, and 3+, with a score of 3+ accepted as HER2/neu-positive. The 2+ positive patients are automatically reflexed to a FISH assay based on previous studies that show these patients have a 25–35% chance of being HER2/neu-positive. However, there have been few detailed investigations into the 0 and 1+ group to determine the false negative rate and the implications of that rate.

I was the senior author representing investigators and patients for the VIRGO trial, an observational study examining the patterns of care in the community for patients with HER2/neu-negative metastatic breast cancer.¹¹ Most patients in the study were HER2/neu-negative and had hormone receptor-negative disease. A very small subset of hormone receptor-positive tumors was allowed, but the number was so small as to be relatively insignificant. We looked at the patients who tested negative for HER2/neu in local laboratories.

Results were either 0 or 1+ by immunohistochemistry or FISH negative.

We determined that the false negative rate was approximately 4%. This rate might not appear to be very high, until one considers that 80% of breast cancer patients in the United States are HER2/neu-negative,¹² and there are well over 200,000 patients diagnosed with breast cancer each year.¹³ In addition, there are more than 2 million surviving breast cancer patients.¹⁴ We calculated that approximately 7,000 women in the United States are being underdiagnosed annually in terms of HER2/neu-positive disease and therefore are not being offered anti-HER2 therapy. Interestingly, in a recent issue of the *ASCO Post*, Dr. Edith Perez discussed her study evaluating the cost effectiveness of expanded reflex testing, in which patients whose tumors were scored as 0, 1+, or FISH negative had additional testing.^{15,16} In this study, a similar percentage of patients, 3%, were found to be false negative. These findings have tremendous implications. Worldwide, if approximately 4% of the population of HER2/neu-negative patients is false negative, then approximately 50,000 patients per year with HER2/neu-positive disease are being underdiagnosed.

Neratinib Versus Lapatinib Plus Capecitabine

Neratinib is a small-molecule tyrosine kinase inhibitor targeting the HER2/neu-positive population. The only tyrosine kinase inhibitor to be commercially available for this population is lapatinib, which was approved by the US Food and Drug Administration (FDA) based on a trial showing that a combination of lapatinib plus capecitabine was superior to capecitabine alone.¹⁷ This combination is considered a standard second-line HER2/neu-positive treatment, while neratinib is a stronger tyrosine kinase inhibitor than lapatinib. While lapatinib inhibits HER1 and HER2, neratinib inhibits HER1, HER2, and HER4 (HER3 lacks a tyrosine kinase domain).

In a study presented at the SABCS, neratinib was compared with the approved combination of lapatinib plus capecitabine.¹⁸ The study found that single-agent neratinib was less effective than lapatinib plus capecitabine. This study began as a phase III trial that was intended to enroll 1,000 patients. However, the trial was presented early after only 230 patients were studied because the PFS, overall response rate, and clinical benefit rate were superior for the combination of capecitabine plus lapatinib versus neratinib. Neratinib has also been associated with significant gastrointestinal toxicity, especially diarrhea. Other “pivotal” trials of neratinib are still in progress.

The AVEREL Trial

The AVEREL trial investigated whether HER2/neu-positive patients with metastatic breast cancer who were receiving standard cytotoxic chemotherapy with docetaxel and trastuzumab would benefit from the addition of bevacizumab, an anti-angiogenesis drug.¹⁹ The recent negative FDA action on bevacizumab in breast cancer has become a contentious issue that we have commented upon at length in a recent review.²⁰ The results of the AVEREL trial were not overwhelmingly in favor of the addition of bevacizumab, however, they raise issues that could be of increasing importance. This study was done because of the results of a first-line clinical trial in metastatic breast cancer in which trastuzumab and bevacizumab were given as a combination and found to be highly beneficial.²¹ The hope was that by giving trastuzumab and bevacizumab, and also adding a very effective form of chemotherapy, there would be additional benefit. In the AVEREL trial, overall response rate as determined by an independent review committee showed a statistically significant benefit in the bevacizumab arm; however, the PFS was just of borderline significance.

Another endpoint was whether the addition of bevacizumab con-

tributed to toxicities. There was no increase in the death rate with the addition of bevacizumab, but there was a tripling of the CHF rate from 0.5% to 1.4%. Since bevacizumab causes hypertension, it is possible that the low rate of cardiotoxicity associated with trastuzumab could be increased in a heart stressed by hypertension.

Another potentially important part of the AVEREL study involves the biomarker data. One of the biggest problems faced by bevacizumab—and the entire anti-angiogenesis field—has been the absence of a predictive marker identifying which patients would benefit from treatment. A number of potential biomarkers were evaluated in the AVEREL trial. Patients who had a greater benefit from bevacizumab had a high VEGF-A plasma level collected in ethylenediaminetetraacetic acid (EDTA) tubes. When a sodium citrate tube was used to measure plasma levels, this association was not shown. This finding will be studied on a broader scale in a new international trial called MERiDIAN. This study will have a similar structure to the pivotal E2100 trial of paclitaxel with or without bevacizumab,²² but looking specifically at the VEGF-A plasma marker as an important endpoint.

The TEACH Trial

This trial was started some years ago, in the era before trastuzumab was used in the adjuvant setting. It included HER2/neu-positive patients who did not receive trastuzumab in the adjuvant setting and had been disease-free for any length of time after surgery (median 2.7 years). The goal of the TEACH trial was to determine whether the late addition of lapatinib might, in a population of patients who had never received anti-HER2 therapy, decrease the rate of recurrence in HER2/neu-positive disease.²³ Seventy percent of the study population entered into the trial less than 4 years after surgery. There was an approximate 3% per year recurrence rate

out to 10 years of follow-up. Overall disease-free survival and overall survival showed no statistical differences between the study arms but with a strong trend in favor of the late addition of lapatinib. An unplanned subset analysis focused on a group of patients who were centrally confirmed to be HER2/neu-positive since we have known for some time that there has been a substantial amount of false-positive local HER2/neu testing. In this trial, the subset of patients who were confirmed to be HER2/neu-positive had a statistically significant benefit for the late addition of lapatinib.

Hormonal Trials

The SWOG 0226 Trial

A trial from the Southwest Oncology Group (SWOG) 0226 included 707 patients who were hormone receptor-positive and HER2/neu-negative.²⁴ Over the years, many combinations of different hormones have been tried, but none has proven superior to single-agent hormonal therapy. This trial studied anastrozole, a first-line hormonal therapy for postmenopausal women with metastatic breast cancer compared with a group who received anastrozole plus fulvestrant. Fulvestrant was given in a loading dose schedule: 500 mg was administered on day 1 and 250 mg was administered on days 14 and 28. Thereafter, maintenance fulvestrant at 250 mg was administered on day 28 of an every-28-day cycle. The combination of fulvestrant plus anastrozole was superior in terms of PFS, but not in terms of overall survival. It should be mentioned that this result contradicts those from the large FACT trial by Bergh, which used similar fulvestrant dosing, presented at the 2009 SABCS.²⁵ In this trial, disease progression was seen in 78.1% of patients who received anastrozole (n=256) and 77.5% of patients who received anastrozole plus fulvestrant (n=258), and the clinical benefit rates were 55.1% for the anastrozole arm and 55% for the combination arm. In patients with measurable disease, the overall response rate, as assessed by

investigators using the RECIST criteria, was 33.6% for the anastrozole group and 31.8% for the fulvestrant plus anastrozole group. In-depth analysis and comparison of the FACT and SWOG 0226 trials will be needed to reconcile the strikingly different findings of the 2 large studies using, essentially, an identical study design.

In another study similar in design to the BOLERO-2 trial,¹ exemestane, instead of being partnered with everolimus (an mTOR inhibitor) was partnered with entinostat, a histone deacetylase inhibitor in 130 patients.²⁶ There was a statistically insignificant trend towards improvement in PFS with entinostat. There was almost a doubling of the PFS, but because the patient population was so small, this finding will not have the impact that the BOLERO-2 trial has had. However, it should increase interest in the concept of the histone deacetylase inhibitors as a class of compounds that might improve the effectiveness of hormonal therapy in metastatic breast cancer.

T-DM1

In addition to pertuzumab, another drug that will likely be submitted eventually for FDA approval is T-DM1, which is a fascinating compound structurally. It is basically a Trojan horse, in which the drug trastuzumab is linked to a toxic chemotherapy drug through a very stable linker. The trastuzumab brings the toxic chemotherapy drug directly into the tumor cell, and it is only within the tumor cell that this linker disintegrates, releasing the toxic chemotherapy drug. T-DM1 is highly effective; I have studied it myself in phase II trials, and found it to be very well tolerated, with minimal hair loss and vomiting.²⁷⁻²⁹

The major trials with T-DM1 were phase II, and we are awaiting completion of the phase III trials (MARIANNE [A Study of Trastuzumab Emtansine (T-DM1) Plus Pertuzumab/Pertuzumab Placebo Versus Trastuzumab [Herceptin] Plus a Taxane in Patients With Metastatic Breast Cancer] and EMILIA [An Open-Label Study of

Trastuzumab-MCC-DM1 (T-DM1) vs Capecitabine+Lapatinib in Patients With HER2-Positive Locally Advanced or Metastatic Breast Cancer]). At the SABCS, and ESMO previously, results were presented for a comparative trial of T-DM1 versus standard chemotherapy with docetaxel and trastuzumab.^{30,31} This randomized phase II trial included 137 patients. The overall response rates and clinical benefit rates were impressive and comparable in the study arms. PFS was 14.2 months in the T-DM1 arm versus 9.2 months in the chemotherapy arm, and the overall response rates were 43% in the T-DM1 arm versus 40% in the chemotherapy arm.³¹ The important differences were in toxicity: 66% of patients lost their hair with docetaxel, but only 1.5% did with T-DM1. Grade 3 or higher adverse events occurred in 89% of patients in the combination arm and 46% of the T-DM1 arm. In the combination arm, 57% developed significant neutropenia versus 7.5% with T-DM1. Diarrhea occurred in 46% of patients in the combination arm versus 11% in the T-DM1 arm. This single agent, T-DM1, has the ability to induce responses that are as good as one of the best chemotherapy plus trastuzumab regimens that we give, and yet does so with minimal toxicity. T-DM1 is potentially an exciting drug that should be moving forward very rapidly toward regulatory approval for the HER2/neu-positive population once confirmatory phase III data are available.

Bisphosphonates and PFS

Most of the drugs that we use to treat breast cancer result in a loss of bone mineral density. There were several studies at the SABCS that examined the effect of bisphosphonates. Previous studies have established that drugs such as zoledronic acid and clodronate have the capability to improve bone mineral density, and there has been evidence presented suggesting an improvement in PFS as well.³² Follow-up data from the Austrian study ABCSG-12 were presented.³³ That study

enrolled premenopausal women, all of whom were rendered postmenopausal with the use of goserelin, which leads to a temporary chemical castration. The patients were then randomized to tamoxifen, a standard drug used in premenopausal women, or to anastrozole, an aromatase inhibitor. There was a second randomization to zoledronic acid or not as part of a 2 by 2 factorial design.

The primary endpoint of this study was to determine whether the aromatase inhibitor would be better than tamoxifen when added to goserelin in a group of young women with early-stage breast cancer treated solely with hormonal therapy. The results showed that neither of those 2 drugs showed any statistically significant improvement over the other. However, the study showed that patients receiving zoledronic acid did not lose bone mineral density, whereas the patients who received placebo did lose bone mineral density. Surprisingly, there was a greater PFS among the women who received zoledronic acid compared with those who received placebo. The zoledronic acid arm also had a 41% reduction in the risk of death (HR, 0.59; $P=.027$).

Similar results were seen in the ZO-FAST trial of postmenopausal women who received zoledronic acid or placebo.³⁴ The primary endpoint of bone protection was shown early with zoledronic acid. The study then examined PFS, which was increased in the zoledronic acid arm.

At the 2010 SABCS, there was much concern caused by results of the AZURE trial of zoledronic acid.³⁵ Overall, this trial showed no benefit in PFS with the use of zoledronic acid; however, a subset of postmenopausal women did appear to benefit. Again, data from subset analyses must be interpreted with caution, however, the current hypothesis is that within a setting of estrogen deprivation—in postmenopausal women (or premenopausal women rendered postmenopausal with goserelin)—zoledronic acid may increase PFS. Those studies all are tantalizing, hinting that perhaps a simple maneuver, such as adminis-

tering zoledronic acid, might not just help prevent bone loss but might also improve PFS and, in the long-term, perhaps even increase overall survival.

Results from studies of 2 other bisphosphonates were also presented. The long-awaited National Surgical Adjuvant Breast and Bowel Project trial B-34 examined the use of clodronate in more than 3,000 patients for benefit in PFS.³⁶ Among the 42% of patients who had completed 3 years of treatment, no significant difference in disease-free survival was observed. Among patients ages 50 years or older, however, clodronate was associated with a significant reduction in the interval without bone metastasis and the interval without metastasis other than bone.

In the GAIN study, the bisphosphonate ibandronate was studied in patients who were not hormonally sensitive patients and who received very intensive chemotherapy, hence a very different population from the Austrian trial, ZO-FAST, B-34, and even AZURE.³⁷ The average age of these women was in the fifties, rather than the sixties as seen in other trials (except for the Austrian trial). Ibandronate did not appear to improve PFS or overall survival. The randomized trial SWOG 0307 randomized early-stage breast cancer patients to zoledronic acid, clodronate, or ibandronate and should provide additional information when mature. However, in the absence of a placebo control arm, PFS and survival outcomes may be difficult to interpret.

Conclusion

Several conclusions can be drawn from the studies presented at the 2011 SABCS. The BOLERO-2 trial provides proof of principle that altering negative cross talk signals between the estrogen receptor pathway and, in this case, the mTOR pathway with everolimus, can lead to an effective therapeutic intervention. The SWOG 0226 trial provides a hint that a combination of the antihormonal agents, anastrozole and fulvestrant, might be superior to anastrozole alone, although

data must be compared and contrasted with the previously published FACT trial of similar design with totally negative results. The trial of entinostat, a histone deacetylase inhibitor, added to exemestane, although smaller than BOLERO-2, raises the question of whether this class of compounds might also improve hormonal effectiveness.

Both pertuzumab and T-DM1 continued at the SABCS 2011 to produce impressive results as they move toward commercial availability. Neratinib failed to improve upon or replace the combination of lapatinib and capecitabine as an effective second-line anti-HER2 therapy. The addition of bevacizumab to a standard trastuzumab/chemotherapy combination in the AVEREL trial showed only modest benefit. Perhaps more importantly in this trial, there was a hint that the elusive goal of finding a biomarker of bevacizumab activity (EDTA plasma VEGF-A) may be within reach. The TEACH trial presented a strong trend suggesting effectiveness of the late institution of lapatinib (average, 2.7 years) after primary breast cancer treatment in trastuzumab-naïve women with early-stage breast cancer. Results of a HER2 testing substudy of the observational VIRGO trial indicate that false-negative local laboratory HER2 testing may be present in 4% of patients. This translates into 7,000 US women and 50,000 women worldwide who may be denied potentially effective anti-HER2 therapy. Further data from the Austrian trial 12, ZO-FAST, and NSABP B-34 provided further tantalizing data suggesting that bisphosphonates, while helping to reduce bone mineral density loss, might also improve efficacy endpoints (PFS and overall survival), at least within the context of a low-estrogen environment.

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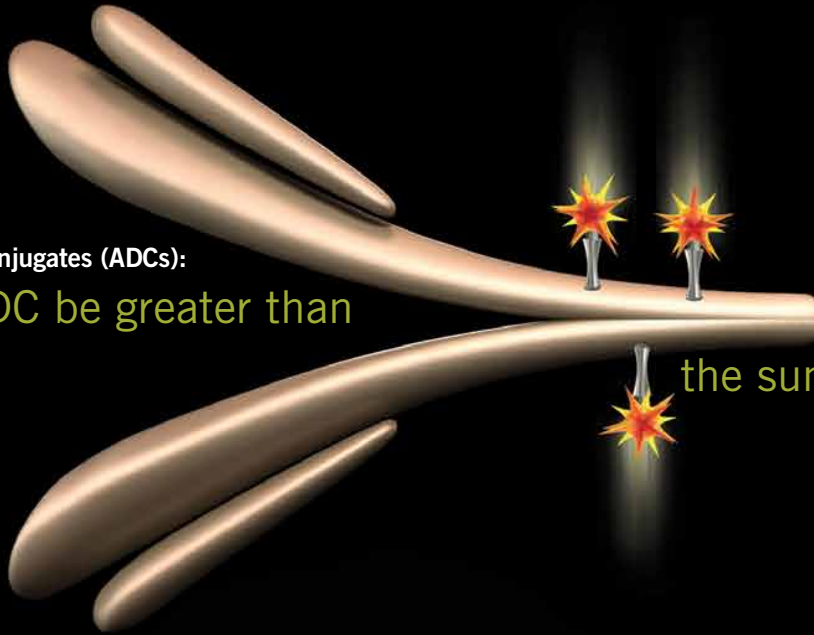
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