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Highlights in Metastatic Breast Cancer From the 2012 San Antonio Breast Cancer Symposium (SABCS)

A Review of Selected Presentations From
the 2012 CTRC-AACR San Antonio Breast Cancer
Symposium (SABCS)
December 4–8, 2012
San Antonio, Texas

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Target Audience

This activity has been designed for medical oncologists, surgical oncologists, and radiation oncologists who contribute to the management of patients with metastatic breast cancer.

Statement of Need/Program Overview

Although advances in early detection and treatment have substantially decreased mortality rates from breast cancer since the early 1990s, for patients with metastatic breast cancer, the 5-year relative survival is less than 25%. The treatment of metastatic breast cancer is complicated by the fact that there is no single standard of care; instead, therapies are often selected based on patient-specific and disease-specific factors. Recent years have seen a number of novel agents approved for this disease, including eribulin mesylate, pertuzumab, and everolimus. During the same time period, the US Food and Drug Administration revoked the approval of bevacizumab for treatment of metastatic breast cancer. This changing treatment landscape is challenging for clinicians. Presentations and posters from the 2012 San Antonio Breast Cancer Symposium offered data from dozens of clinical trials in metastatic breast cancer. Awareness of these new data can help clinicians devise the best personalized management approaches for their patients.

Educational Objectives

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

- Discuss efficacy and safety data from new and emerging agents for the treatment of metastatic breast cancer
- Recognize patient characteristics that help determine management strategies
- Incorporate newly approved agents into treatment regimens to improve response and survival outcomes of metastatic breast cancer patients
- Identify future research directions and novel targets in the treatment of metastatic breast cancer

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Highlights in Metastatic Breast Cancer From the 2012 San Antonio Breast Cancer Symposium (SABCS)

S6-6 A Phase III, Open-Label, Randomized, Multicenter Study of Eribulin Mesylate Versus Capecitabine in Patients With Locally Advanced or Metastatic Breast Cancer Previously Treated With Anthracyclines and Taxanes[1]

PA Kaufman, A Awada, C Twelves, L Yelle, EA Perez, J Wanders, MS Olivo, Y He, CE Dutcus, J Cortés

As demonstrated in the phase III EMBRACE (Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389) trial, eribulin mesylate is the only chemotherapeutic agent with a proven survival benefit for patients with heavily pretreated metastatic breast cancer.[2] The EMBRACE trial showed a 2.5-month improvement in overall survival (OS) with eribulin in comparison to physician's treatment of choice and led to approval of the agent in the United States in 2010 for patients who have received at least 2 prior chemotherapy regimens for late-stage disease.[3] Eribulin is an analog of halichondrin B, which was originally isolated from a marine sponge.[4-6] Unlike other microtubule inhibitors, eribulin targets the positive end of the microtubule, potently inhibiting microtubule polymerization and lengthening with no effect on microtubule shortening. Preclinical data suggest that it leads to a potent and irreversible mitotic block.[7]

Kaufman and colleagues reported the first results from a global, randomized, open-label, phase III study evaluating eribulin versus capecitabine in 1,102 enrolled patients.[1] The patients had received 2 or fewer prior chemotherapeutic regimens for advanced disease, and a maximum of 3 regimens total. All patients had previously received anthracycline and taxane therapy. Patients had adequate organ function and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2.

After stratification based on human epidermal growth factor receptor 2 (HER2) status and geographical region, patients were randomized 1:1 to receive either eribulin mesylate (1.4 mg/m^2 on days 1 and 8; n=554) or capecitabine (1,250 mg/m^2 twice daily on days 1–14; n=548) on a 3-week schedule. The study design included 2 co–primary endpoints of OS and progression-free survival (PFS), with secondary endpoints including quality of life, objective response rate (ORR), and 1-year, 2-year, and 3-year survival. The study was powered as a superiority trial with a planned enrollment of 1,100 patients and a final analysis at 905 events for OS. Statistical significance was calculated to require a final *P* value of less than or equal to 0.032 for OS, or a *P* value of less than .01 for PFS, along with a hazard ratio (HR) of less than 1 for overall survival.

Patient characteristics were well balanced between the 2 arms. Approximately 20%, 50%, and 30% of patients received first-, second-, or third-line chemotherapy on-study, respectively. Approximately 85% of patients had visceral metastases, and approximately 70% of patients had HER2-negative disease. Approximately 25% of patients (n=284) had triple-negative breast cancer (TNBC).

The study failed to demonstrate a significant improvement in either of its 2 primary endpoints. OS was 15.9 months with eribulin versus 14.5 months with capecitabine (HR, 0.879; 95% confidence interval [CI], 0.770–1.003; *P*=.056; Figure 1). Although this difference was not significant, eribulin demonstrated a positive trend in survival, and the survival curve separated early. Survival at 1, 2, or 3 years was numerically superior for eribulin but failed to reach significance. PFS was 4.1–4.2 months for both arms by investigator review (HR, 1.079; 95% CI, 0.932–1.250; *P*=.305) and independent review (HR, 0.977; 95% CI, 0.857–1.114; *P*=.736). Response rates were also similar between the 2 treatment arms, with ORRs for eribulin versus capecitabine of 11% versus 12%, respectively, by independent review and 16% versus 20%, respectively, by investigator review. Medication exposure was comparable between the 2 arms. Prespecified subgroup analyses suggested that eribulin was favored in patients with HER2-negative disease (HR, 0.838; 95% CI, 0.715–0.983), estrogen receptor (ER)-negative disease (HR, 0.779; 95% CI, 0.635–0.955), and TNBC (HR, 0.702; 95% CI, 0.545–0.906; Figure 2). This study was the first to demonstrate that eribulin is valid for both first-line and second-line treatment of metastatic breast cancer.

The majority of patients in both arms experienced an adverse event (AE). Serious AEs were reported in 17.5% of patients receiving eribulin and 21.1% of patients receiving capecitabine, and treatment-related AEs leading to dose modification were comparable in both arms. Fatal AEs occurred in 4.8% and 6.6% of patients who received eribulin or capecitabine, respec-

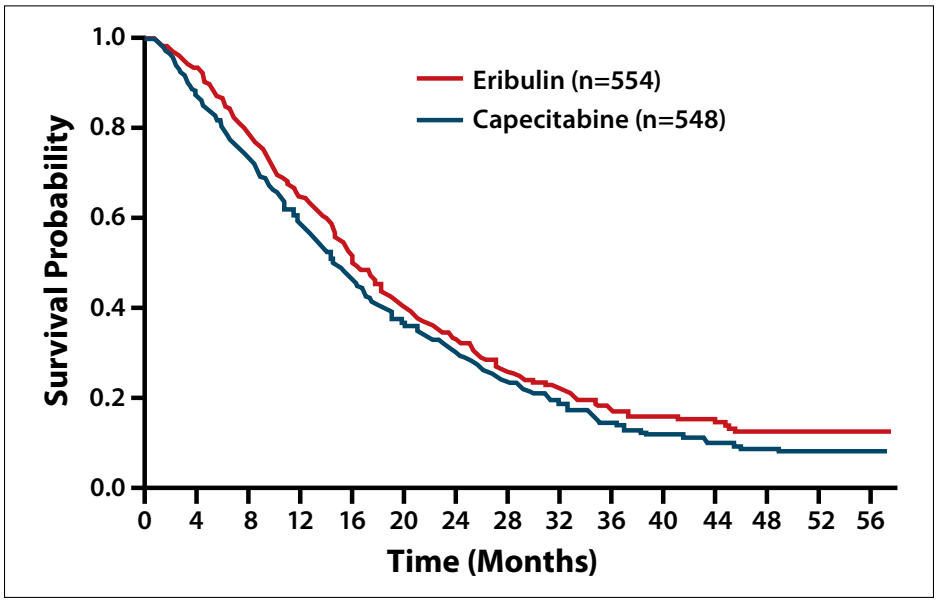

Figure 1. In a phase III trial of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes, overall survival was 15.9 months with eribulin mesylate versus 14.5 months with capecitabine (hazard ratio, 0.879; 95% confidence interval, 0.770–1.003; *P*=.056). Adapted from Kaufman PA et al. Paper presented at the 2012 San Antonio Breast Cancer Symposium; December 4-8, 2012; San Antonio, TX. Abstract S6-6.[1]

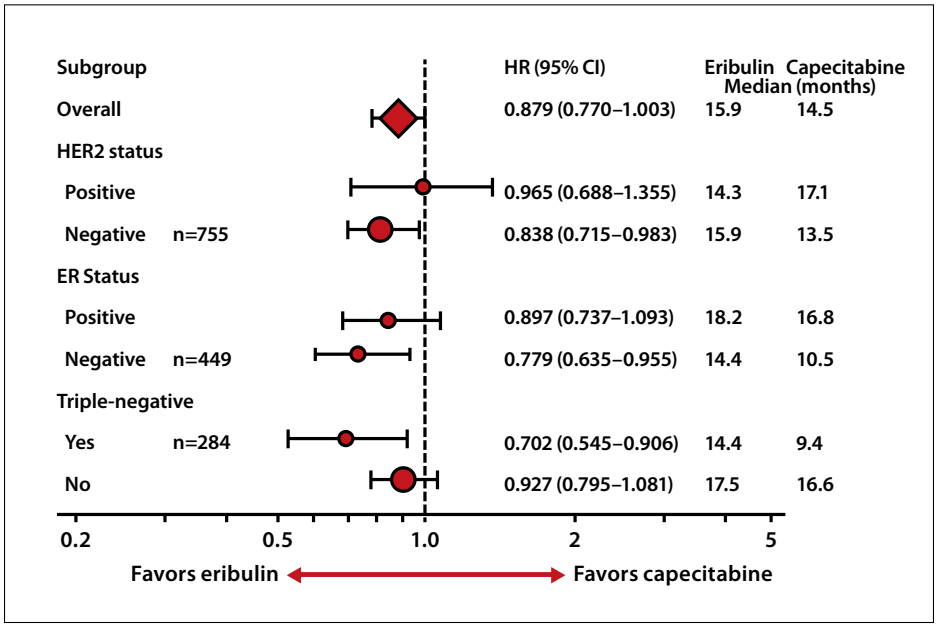

Figure 2. In a phase III trial of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes, prespecified subgroup analyses suggested that eribulin was favored in patients with HER2-negative disease, ER-negative disease, and triple-negative breast cancer. CI=confidence interval; ER=estrogen receptor; HER2=human epidermal growth factor receptor 2; HR=hazard ratio. Adapted from Kaufman PA et al. Paper presented at the 2012 San Antonio Breast Cancer Symposium; December 4-8, 2012; San Antonio, TX. Abstract S6-6.[1]

tively. No new safety concerns were raised by the AE profiles for either treatment. Hematologic side effects were common with eribulin, with 46% of patients developing grade 3/4 neutropenia, but with a febrile neutropenia rate of only 2%. The most common non-hematologic AEs of any grade occurring in 20% or more of patients were alopecia (35%) and nausea (22%) in the eribulin arm and hand-foot syndrome (45%),

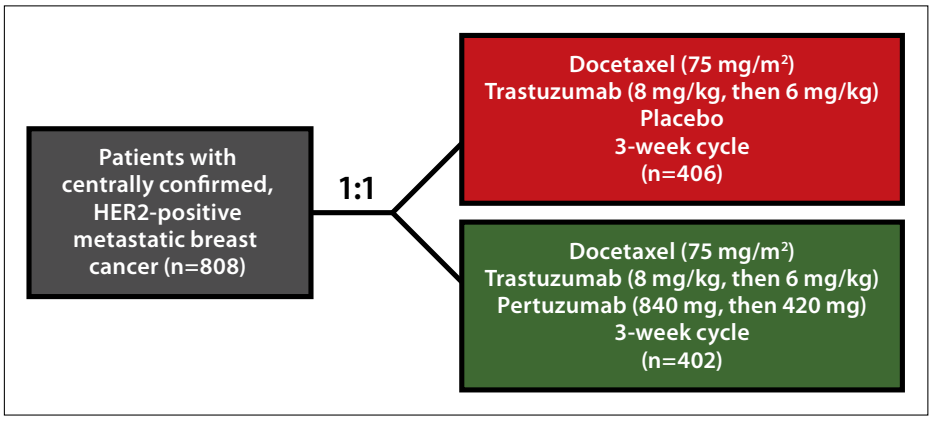

Figure 3. Study design of the phase III CLEOPATRA trial. At least 6 cycles of docetaxel were recommended. Docetaxel was escalated to 100 mg/m² if tolerated. CLEOPATRA=Clinical Evaluation of Pertuzumab and Trastuzumab. Data from Baselga J et al. *N Engl J Med*. 2012;366:109-119.[11]

diarrhea (29%), and nausea (24%) in the capecitabine arm. Grade 3/4 AEs occurring in either arm in at least 4% of patients included asthenia (<5%) and peripheral neuropathy (4%) in the eribulin arm and hand-foot syndrome (14%), diarrhea (5%), and asthenia (4%) in the capecitabine arm.

P5-18-26 Confirmatory Overall Survival (OS) Analysis of CLEOPATRA: A Randomized, Double-Blind, Placebo-Controlled Phase III Study With Pertuzumab (P), Trastuzumab (T), and Docetaxel (D) in Patients (pts) With HER2-Positive First-Line (1L) Metastatic Breast Cancer (MBC)[8]

SM Swain, S-B Kim, J Cortés, J Ro, V Semiglazov, M Campone, E Ciruelos, J-M Ferrero, A Schneeweiss, A Knott, E Clark, G Ross, MC Benyunes, J Baselga

Pertuzumab is a humanized monoclonal antibody that binds to HER2 at a different site from trastuzumab.[9] In contrast to trastuzumab, pertuzumab preferentially inhibits the formation of HER2-HER3 dimers. Combining the 2 antibodies was shown to induce synergistic antitumor activity in HER2-positive cell lines and xenograft models.[9,10] The phase III CLEOPATRA (Clinical Evaluation of Pertuzumab and Trastuzumab) trial randomized 808 patients with treatment-naïve metastatic breast cancer (MBC) to treatment every 3 weeks with trastuzumab (8 mg/kg loading dose followed by 6 mg/kg thereafter) and docetaxel (75 mg/m²) plus either pertuzumab (840 mg loading dose followed by 420 mg thereafter) or placebo (Figure 3).[11] Docetaxel was escalated to 100 mg/m² if tolerated. The addition of pertuzumab significantly improved PFS over placebo (18.5 months vs 12.4 months; HR, 0.62; 95% CI, 0.51–0.75; *P*<.0001). An initial OS analysis, performed after the occurrence of 43% of the OS events planned for the final analysis, showed a trend in favor of the antibody combination (HR, 0.64; 95% CI, 0.47–0.88), but the results were immature. In response to a formal request from health authorities, a second interim analysis was performed with a median follow-up of 30 months, representing an additional year of follow-up, after 69% of the planned events (267 deaths) for the final analysis had occurred.[8] The analysis revealed a significant increase in OS for patients who received pertuzumab relative to placebo (HR, 0.66; 95% CI, 0.52–0.84; *P*=.0008). Median OS in the pertuzumab arm was not yet reached versus 37.6 months for the placebo control arm, and the improved OS was observed in all predefined subgroups, with the exception of patients with non-visceral disease. An exploratory analysis of investigator-assessed PFS showed improvement with pertuzumab compared with placebo (18.7 months vs 12.4 months; HR, 0.69; 95% CI, 0.58–0.81), consistent with the original PFS results. Because the second interim OS analysis crossed the O'Brien-Fleming stopping boundary, the results were considered statistically significant and presented as the confirmatory OS analysis. With an additional year of follow-up, no new safety signals beyond those in the primary analysis were revealed; hence no cumulative or late toxicity was observed with pertuzumab treatment in this context. Combination treatment with pertuzumab did not increase the incidence of cardiac AEs, including left ventricular systolic dysfunction (LVSD), compared with placebo. The authors concluded that the combination of pertuzumab plus trastuzumab plus docetaxel can be considered a standard of care for patients with HER2-positive, treatment-naïve MBC.

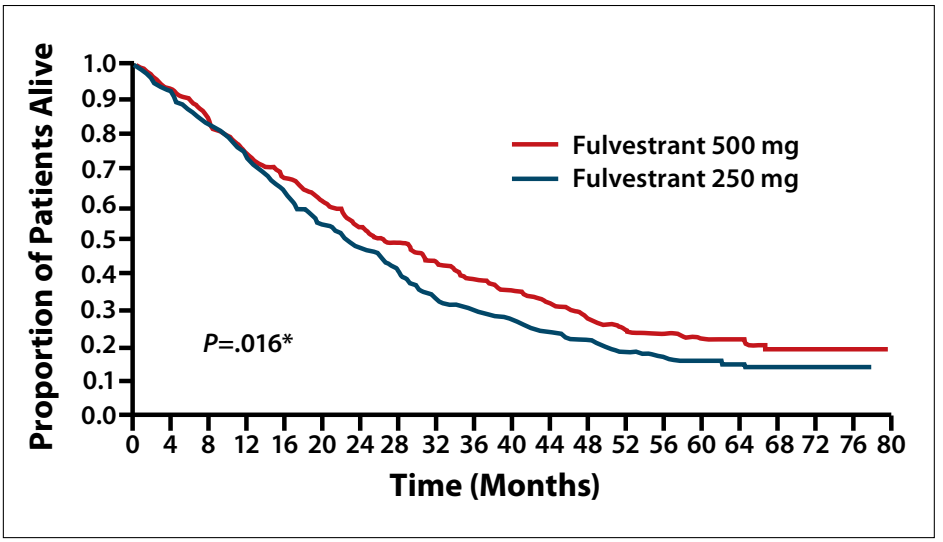

Figure 4. Overall survival in the phase III CONFIRM trial, which compared fulvestrant at 500 mg and 250 mg. *The *P* value of .016 is nominal and is not considered statistically significant. CONFIRM=Comparison of Faslodex In Recurrent or Metastatic Breast Cancer. Adapted from Di Leo A et al. Final analysis of overall survival for the phase III CONFIRM trial: fulvestrant 500 mg versus 250 mg. Paper presented at the 2012 San Antonio Breast Cancer Symposium; December 4-8, 2012; San Antonio, TX. Abstract S1-4.[12]

S1-4 Final Analysis of Overall Survival for the Phase III CONFIRM Trial: Fulvestrant 500 mg Versus 250 mg[12]

A Di Leo, G Jerusalem, L Petruzelka, R Torres, IN Bondarenko, R Khasanov, D Verhoeven, JL Pedrini, I Smirnova, MR Lichinitser, K Pendergrass, S Garnett, Y Rukazenkov, M Martin

Dr. Angelo Di Leo and colleagues presented final results of the phase III CONFIRM (Comparison of Faslodex In Recurrent or Metastatic Breast Cancer) trial, which compared 2 doses of fulvestrant in menopausal women with advanced, ER-positive breast cancer.[13] Patients received either 250 mg of fulvestrant plus a second placebo injection (n=374) or 2 injections of 250 mg fulvestrant (n=362) on days 0, 14, 28, and every 28 days thereafter. Eligible patients had relapsed within 1 year of the completion of endocrine therapy. For patients who progressed more than 1 year after the completion of adjuvant endocrine therapy, or for patients with de novo advanced breast cancer, previous first-line endocrine therapy was mandatory for potential entry into the CONFIRM trial.

The patients' median age was 61 years. Approximately 70% had progesterone receptor–positive disease, and slightly more than half had visceral involvement. Study medication was the first-line treatment for approximately half of patients and the second-line treatment for the other half. As previously reported, the primary endpoint of median PFS was prolonged from 5.5 months to 6.5 months with the higher dose of fulvestrant (HR, 0.80; 95% CI, 0.68–0.94; *P*=.006).[13] OS analysis was performed at the same time as the PFS analysis, after 50% of the events had occurred. Although patients receiving 500 mg of fulvestrant showed a longer median time until death (25.1 months vs 22.8 months), the result was not significant (HR, 0.84; 95% CI, 0.69–1.03; *P*=.091).

Based on the numerical superiority of the OS data for the higher dose of fulvestrant, the study statistical plan was amended to include a second, exploratory analysis to be performed upon the occurrence of 75% of events.[12] Due to the original statistical plan, no alpha was retained, and no adjustment for multiplicity was feasible for the second analysis. During the survival follow-up phase, patient monitoring every 3 months was continued until data cutoff, serious AEs were reported for patients still receiving the study treatment, and data on the first subsequent systemic breast cancer therapy and response were collected. At the time of the second data cutoff, fewer than 4% of patients in each arm were still on study treatment, and approximately 10–12% were still alive but not on study treatment. In the 500 mg and 250 mg fulvestrant arms, 72.1% and 78.3% of patients had died, and 9.1% and 8.0% were lost to follow-up, respectively. The exploratory analysis revealed a new HR of 0.81 (95% CI, 0.69–0.96; Figure 4). The *P* value of .016 is regarded as a nominal value and cannot be considered significant. Nonetheless, the authors underscored the consistency between the 2 survival analyses, which yielded HR values of 0.84 at 50% maturity and 0.81 at 75% maturity.

The influence of post-study therapy was assessed with the information available from approximately two-thirds

of the study participants. More than 90% of patients had received subsequent therapy after progression on fulvestrant, with 59% of patients in both arms receiving chemotherapy and 31–35% receiving non-fulvestrant endocrine therapy. The 2 arms showed similar antitumor activity, with an ORR of 8% in each arm, and a clinical benefit that was slightly higher for patients who had received the lower dose of fulvestrant (41% vs 33%). Crossover to 500 mg of fulvestrant was offered only after the PFS analysis had been performed; hence, the study showed a low crossover rate of 2.1%.

Rates of serious AEs were similar in the 2 arms: 9.7% in patients who had received the higher dose and 7.2% in patients who had received the lower dose. Treatment-related serious AEs were reported for 8 patients (2.2%) in the higher dose arm and for 4 patients (1.1%) in the lower dose arm. Fatal AEs were reported for 5 patients in the 500 mg arm versus 7 patients in the 250 mg arm.

P1-12-02 Results of a Phase 2, Multicenter, Single-Arm Study of Eribulin Mesylate as First-Line Therapy for Locally Recurrent or Metastatic HER2-Negative Breast Cancer[14]

L Vahdat, L Schwartzberg, S Glück, J Rege, S Zhou, D Cox, J O'Shaughnessy

A phase II trial was designed to evaluate the ORR following treatment with first-line eribulin mesylate monotherapy in patients with locally recurrent or metastatic, HER2-negative breast cancer.[14] Secondary objectives included safety and tolerability, time to first response, duration of response (DOR), and PFS. Eligible patients had at least 1 measurable lesion based on Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 criteria and an ECOG PS of 0–2, with at least 12 months elapsed since receiving neoadjuvant or adjuvant chemotherapy. HER2-negative status was determined by either fluorescence in situ hybridization (FISH) or immunohistochemistry. Eribulin mesylate (1.4 mg/m^2) was administered intravenously on days 1 and 8 of each 3-week cycle, with 6 cycles planned.

Enrolled patients had a median age of 56.5 years (range, 31–78 years). Prior therapies included an anthracycline or taxane in 52.1% and 47.9% of patients, respectively, and 37.5% of patients had received prior therapy that did not contain these agents. Twenty-six patients (54.2%) received all 6 planned cycles of eribulin mesylate, and a median of 6 cycles were administered per patient (range, 1–17). An objective partial response (PR) was observed in 13 of 48 enrolled patients (27.1%), of whom 47 had at least 1 post-baseline assessment. Of these 13 patients with PRs, the median time to first response was 1.4 months (95% CI, 1.31–2.69 months) and the median DOR was 7.4 months (95% CI, 3.29–not evaluable). Among the 35 patients with ER-positive disease, 10 (28.6%) achieved an objective response. In the small subgroup of 10 patients with TNBC, 3 (30%) achieved an objective response. Median PFS was 5.9 months (95% CI, 3.48–7.39 months). The majority of patients showed a reduction in the total sum of target lesion diameters from baseline to post-baseline nadir, based on RECIST 1.1 criteria.

The most common treatment-related, treatment-emergent AEs of any grade occurring in more than 25% of patients included alopecia (75.0%), neutropenia (72.9%), fatigue (54.2%), nausea (47.9%), peripheral neuropathy (47.9%), anemia (37.5%), and constipation (31.3%). Grade 3 or 4 events included neutropenia (50.0%), peripheral neuropathy (12.5%), anemia (4.2%), and fatigue (2.1%). Treatment-related, treatment-emergent serious AEs occurred in 8.3% of patients and included febrile neutropenia (4.2%), neutropenia (4.2%), and leukopenia (2.1%). Treatment-related, treatment-emergent AEs leading to dose delay, reduction, or discontinuation occurred in 54.2% of patients. Final study results are expected by the end of 2013.

P6-04-02 Final Progression-Free Survival Analysis of BOLERO-2: A Phase III Trial of Everolimus for Postmenopausal Women With Advanced Breast Cancer[15]

M Piccart, J Baselga, S Noguchi, H Burris, M Gnant, G Hortobagyi, P Mukhopadhyaya, T Taran, T Sahmoud, H Rugo

In the phase III, double-blind BOLERO-2 (Breast Cancer Trials of Oral Everolimus) trial, postmenopausal patients with HR-positive breast cancer that progressed or recurred after treatment with a nonsteroidal aromatase inhibitor were randomized to receive the steroidal inhibitor exemestane (25 mg once daily), plus either the mammalian target of rapamycin (mTOR) inhibitor everolimus (10 mg once daily; n=485) or placebo (n=239).[16] Patients were stratified based on the presence or absence of visceral metastases and sensitivity or insensitivity to previous hormonal therapy. Secondary endpoints included OS, safety, bone turnover, and ORR. Interim analyses had demonstrated a significant increase in the primary endpoint of PFS for patients receiving the combination treatment. Dr. Martine Piccart and colleagues presented results from the final, protocol-defined PFS analysis after a median 18 months of follow-up.[15]

PFS analysis by local radiologic assessment showed a risk reduction of 55% for patients receiving everolimus relative to placebo (HR, 0.45; 95% CI, 0.38–0.54;

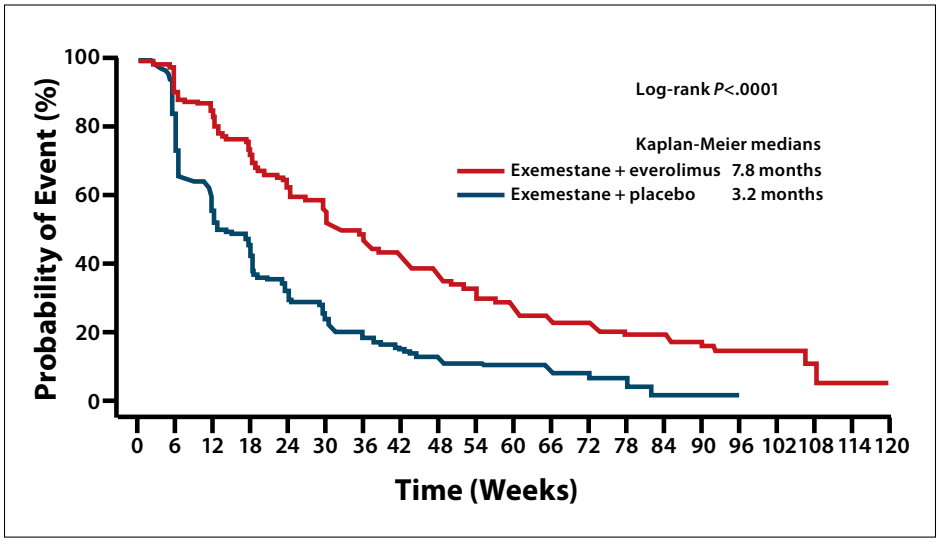

Figure 5. In the final progression-free survival analysis of the BOLERO-2 trial, progression-free survival was extended from 3.2 months in the placebo arm to 7.8 months in the everolimus arm. BOLERO-2=Breast Cancer Trials of Oral Everolimus. Adapted from Piccart M et al. Poster presented at the 2012 San Antonio Breast Cancer Symposium; December 4-8, 2012; San Antonio, TX. Poster P6-04-02.[15]

P<.0001). PFS was extended from 3.2 months for the placebo arm to 7.8 months for the everolimus arm (Figure 5). PFS analysis by central radiologic assessment showed a risk reduction of 62% with everolimus treatment (HR, 0.38; 95% CI, 0.31–0.48; *P*<.0001). PFS was 4.1 months for patients receiving placebo versus 11.0 months for patients receiving everolimus. Based on local investigator analysis, a consistent PFS benefit was discerned for prospectively defined subgroups based on local investigator or central review, including patients with visceral metastases (HR, 0.47; 95% CI, 0.37–0.60), patients without visceral metastases (HR, 0.4; 95% CI, 0.31–0.55), and patients with metastases present in the bones only (HR, 0.33; 95% CI, 0.21–0.53). In patients with visceral metastases, PFS improved with everolimus plus exemestane regardless of ECOG PS. PFS was also improved by the combination treatment in patients whose disease recurred after neoadjuvant or adjuvant therapy (HR, 0.39; 95% CI, 0.25–0.62), suggesting efficacy as first-line therapy for advanced breast cancer. Preliminary OS analysis after 200 deaths and with data that were not mature showed no significant difference in OS between the 2 treatment arms (25.4% with placebo vs 32.2% with everolimus; HR, 0.77; 95% CI, 0.57–1.04). AEs were consistent with the drug's known safety profile, and the most common grade 3 or 4 AEs were stomatitis (8%), hyperglycemia (5%), and fatigue (4%).[17,18] Pneumonitis and interstitial lung disease were observed in the everolimus arm but not the placebo arm. The authors concluded that the clinical benefit observed with everolimus and exemestane in this patient population may lead to a treatment paradigm shift.

S1-6 Results of a Randomized Phase 2 Study of PD 0332991, a Cyclin-Dependent Kinase (CDK) 4/6 Inhibitor, in Combination With Letrozole Vs Letrozole Alone for First-Line Treatment of ER+/HER2- Advanced Breast Cancer (BC)[19]

RS Finn, JP Crown, I Lang, K Boer, IM Bondarenko, SO Kulyk, J Ettl, R Patel, T Pinter, M Schmidt, Y Shparyk, AR Thummala, NL Voytko, A Breazna, ST Kim, S Randolph, DJ Slamon

Cyclin-dependent kinases (CDKs) play a critical role in regulating cell cycle progression and are a novel target in cancer therapy.[20] PD 0332991 is a highly selective, oral inhibitor of CDKs 4 and 6 that has been shown to arrest cells in phase G1 of the cell cycle.[21] Normally, the retinoblastoma protein is hyperphosphorylated during the G1 phase, which allows cell cycle progression into the S phase; however, by binding to CDKs 4 and 6, PD 033291 prevents this hyperphosphorylation of retinoblastoma protein, thus inducing G1 cell cycle arrest. The molecule showed activity in a large panel of breast cancer cell lines, with the greatest activity observed in luminal, ER-positive, HER2-negative cell lines and those with HER2 amplification. The most resistant lines were non-luminal or triple-negative. Synergistic activity was observed when PD 0332991 was combined with tamoxifen.

Based on these observations, a phase I/II study was initiated to assess the combination of PD 033291 plus letrozole in postmenopausal women with advanced breast cancer.[19] The phase I portion yielded a recommended

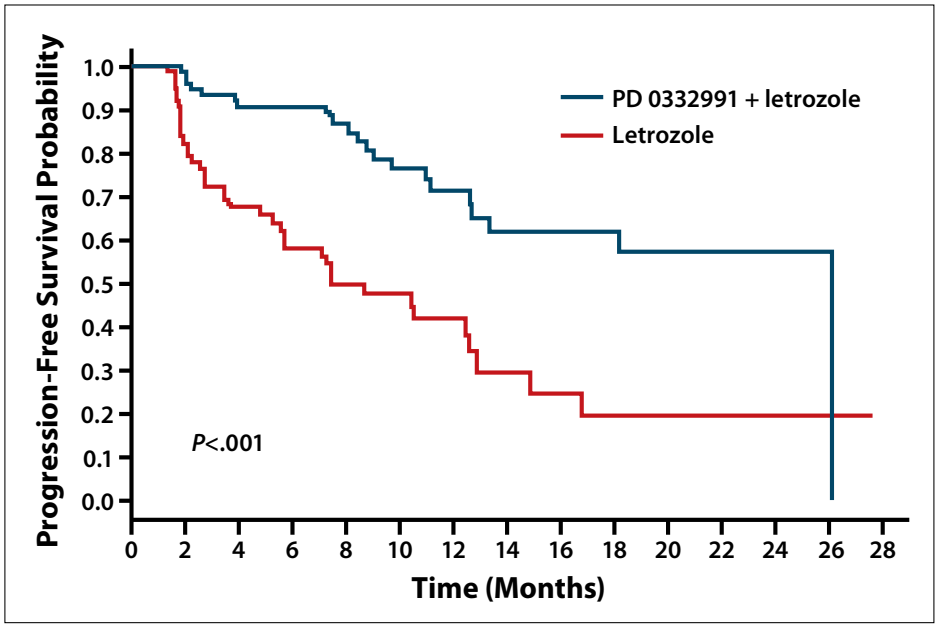

Figure 6. In a randomized phase II study, the addition of PD 0332991, a cyclin-dependent kinase 4/6 inhibitor, to letrozole improved progression-free survival over letrozole alone for first-line treatment of ER-positive/HER2-negative advanced breast cancer. ER=estrogen receptor; HER2=human epidermal growth factor receptor 2. Adapted from Finn RS et al. Paper presented at the 2012 San Antonio Breast Cancer Symposium; December 4-8, 2012; San Antonio, TX. Abstract S1-6.[19]

phase II dose of PD 0332991 at 125 mg daily on days 1–21 of a 28-day schedule plus letrozole 2.5 mg daily.[22] The phase II design consisted of 2 parts. Part 1 (n=66) enrolled patients with ER-positive, HER2-negative breast cancer; patients were randomized 1:1 to receive letrozole with or without PD 0332991. Part 2 (n=99) enrolled patients with the same disease characteristics as well as cyclin D1 amplification based on FISH or loss of p16. Patients were stratified based on disease sites (visceral vs bone-only vs other) and disease-free interval (DFI) since prior therapy (12 months or less versus greater than 12 months). The study had a primary endpoint of PFS and was designed to detect a 50% improvement in PFS, from 9 months to 13.5 months, with 80% power.

Interim Analysis One included data from part 1 only and showed an improvement in PFS for the combination treatment relative to letrozole only (HR, 0.35; *P*=.006).[23] Interim Analysis Two included combined data from parts 1 and 2 and encompassed 50% of total events and 57 PFS events, with a data cutoff of July 2012. The final analysis also used combined data from both parts of phase II and required 114 PFS events. All patients were required to have measurable disease based on RECIST 1.0 criteria, ECOG PS of 0 or 1, adequate blood counts and organ function, and no prior or current brain metastases.

Dr. Richard Finn and colleagues presented results of Interim Analysis Two, which included combined data from parts 1 and 2 of the phase II portion of the study. Patient characteristics were generally well balanced between the patients receiving combined treatment (n=84) versus those receiving letrozole only (n=81).[19] Approximately half of the patients had de novo metastatic disease, and the remainder of patients had received prior adjuvant therapy consisting of chemotherapy (40–46%) or hormonal therapy (31–35%). The analysis demonstrated an ORR of 34% for PD 0332991 plus letrozole versus 26% with letrozole only. Approximately two-thirds of the patients in both arms had measurable disease, and in these patients, the experimental combination yielded a greater increase in ORR relative to letrozole only (45% vs 31%). The clinical benefit rate improved with the addition of PD 0332991, from 44% to 70%. The addition of the kinase inhibitor also significantly improved the median PFS from 7.5 months with letrozole alone to 26.1 months with the combination (HR, 0.37; 95% CI, 0.21–0.63; *P*<.001; Figure 6). Median DOR was 8.9 months (range, <1–25.9 months) for patients receiving PD 0332991 versus 5.1 months (range, <1–29.0 months) for letrozole monotherapy.

Patients receiving the CDK inhibitor had more dose interruptions, cycle delays, or dose reductions; however, the majority of drug discontinuations occurred due to disease progression (26%), with only 10% of patients discontinuing due to an AE. The toxicity profile was very manageable. As expected from the experimental drug's mechanism of action, the incidence of leukopenia and neutropenia increased, with grade 3/4 leukopenia occurring in 51% of patients (vs 1% of patients receiv-

ing monotherapy) and grade 3/4 neutropenia occurring in 14% of patients (vs 0% with monotherapy). However, these events were not considered clinically important. There was no evidence of neutropenic fever, and no growth factors were used in the study. Other treatment-related AEs of any grade, occurring in 10% or more of patients, were reported as follows in the combination versus monotherapy arms, respectively: anemia (24% vs 0%), fatigue (19% vs 13%), alopecia (18% vs 3%), hot flush (17% vs 10%), arthralgia (16% vs 10%), nausea (14% vs 1%), and thrombocytopenia (12% vs 0%), with the vast majority of these events being grade 1 or 2.

P6-11-14 Post-Hoc Safety and Tolerability Assessment in Patients Receiving Palliative Radiation During Treatment With Eribulin Mesylate for Metastatic Breast Cancer[24]

DA Yardley, L Vahdat, J Rege, J Cortés, J Wanders, C Twelves

In 2 clinical studies of eribulin mesylate in patients with locally recurrent or metastatic breast cancer, palliative radiation therapy (RT) was permitted for treating a variety of indications.[2,25] Because many chemotherapy agents act as radiation sensitizers, the safety and tolerability of palliative RT in patients receiving eribulin mesylate were assessed. The post-hoc, pooled analysis included patients from studies 211 (phase II) and 305 (phase III) who received eribulin.[24] The analysis excluded patients who had received RT within the 3 weeks prior to initiation of eribulin or RT encompassing greater than 30% of bone marrow.

Eribulin mesylate was administered intravenously on days 1 and 8 of each 21-day cycle. Palliative RT was allowed in both studies for bone pain, bronchial obstruction, and ulcerating skin lesions. The total field for palliative RT could involve a maximum of 10% of total bone marrow. The irradiated lesion was to be excluded for assessing tumor response. Eribulin treatment was delayed during RT and was resumed following resolution of RT-related toxicities. In the post-hoc analysis, 13 patients from study 211 and 31 patients from study 305 had received palliative RT, whereas no palliative RT was administered to the remaining 278 and 472 patients in the 2 studies, respectively. HER2-negative disease was reported in 76.8% of patients in the subgroup that did not receive palliative RT and in 81.8% of patients who received RT. Fifty-nine percent of patients received a radiation dose of at least 10 Gray. The most common sites of palliative RT were the back/spine (19%) and the leg/hip (17%). Thirty-three patients received palliative RT for up to 7 days, and 11 patients received palliative RT for 8–20 days.

Important differences in AE profiles for the 2 subgroups did not emerge. The most common AEs reported in the subgroups that did or did not receive palliative RT, respectively, were neutropenia (50% vs 55%), alopecia (48% vs 51%), nausea (43% vs 40%), fatigue (39% vs 32%), and asthenia (27% vs 32%). Localized events that occurred more frequently in the palliative RT subgroup included bone pain (27% vs 15%), back pain (27% vs 10%), and musculoskeletal pain (14% vs 8%). This analysis did not demonstrate a difference in the AE profiles in patients receiving eribulin mesylate with palliative RT versus without palliative RT.

P5-18-20 Phase II Study of Pertuzumab, Trastuzumab, and Weekly Paclitaxel in Patients With Metastatic HER2-Overexpressing Metastatic Breast Cancer[26]

F Datko, G D'Andrea, M Dickler, S Goldfarb, M Theodoulou, D Lake, M Fornier, S Modi, N Sklarin, E Comen, D Gajria, T Traina, T Gilewski, ME Moynahan, P Drullinsky, D Atieh-Graham, C Wasserheit-Leiblich, C Murphy, N Hamilton, M Chen, A Lau, S Patil, J Liu, S Chandarlapaty, L Norton, C Hudis, C Dang

The phase III CLEOPATRA trial demonstrated that the addition of pertuzumab to trastuzumab plus docetaxel prolonged PFS in patients with HER2-positive MBC.[11] With respect to taxane therapy, weekly paclitaxel appears to provide superior outcomes compared to paclitaxel every 3 weeks and may be less toxic than docetaxel.[27,28] Therefore, an ongoing phase II study was designed to evaluate the safety and efficacy of weekly paclitaxel plus trastuzumab and pertuzumab.[26] The trial has a planned enrollment of 68 patients with HER2-positive MBC who had received 1 or no prior treatments in the metastatic setting. Treatment consists of weekly paclitaxel (80 mg/m^2), trastuzumab every 3 weeks (loading dose 8 mg/kg followed by 6 mg/kg thereafter), and pertuzumab every 3 weeks (loading dose 840 mg followed by 420 mg thereafter). The primary endpoint is PFS at 6 months, with secondary endpoints of response, safety (including cardiac events), and tolerability. Left ventricular ejection fraction (LVEF) is monitored by echocardiography every 3 months. Defined cardiac events include symptomatic LVSD, non-LVSD cardiac death, and probable cardiac death.

Out of 50 patients enrolled as of November 12, 2012, 36 were eligible for 6-month PFS assessment and 33 were evaluable. The median age was 53 years (range, 29–84 years), and all patients had an ECOG PS of 0 or 1. Measurable disease was present in 26 patients (79%). Eighteen patients (55%) had received prior adjuvant therapy, and 8 patients (24%) had received 1 prior therapy in

the metastatic setting. PFS at 6 months was 76% (25 of 33 evaluable patients) and included 3 patients (9%) with a complete response (CR), 14 patients (42%) with a PR, and 8 patients (24%) with stable disease (SD). No unexpected toxicities were observed. Eight treatment-related grade 3/4 AEs were reported, most of which resolved with treatment or cessation of the study drug. One case each of grade 3 neutropenia, cellulitis and edema, and blurry vision led to paclitaxel dose reduction or discontinuation. As of the study cutoff date, no cardiac events had occurred. One patient had asymptomatic, grade 2 LVEF decline. Ejection fraction declined from 57% to 47% at 9 months in a 61-year-old patient with a history of cardiomyopathy controlled by medication. This patient was taken off the study with no additional intervention required, and her ejection fraction was at 44% on 3-month follow-up.

P6-09-06 Family Members' Burden in Patients With Metastatic and Early Stage Breast Cancer[29]

Y Wan, X Gao, S Mehta, Z Zhang, C Faria, L Schwartzberg

A retrospective study was undertaken to compare the productivity losses and associated costs to family members of patients with early-stage breast cancer (EBC) versus MBC.[29] Data from 2005–2009 were taken from the Thomson Reuters MarketScan Health and Productivity Management database. Included patients had EBC or MBC with no other tumors and had continuous medical insurance for 12 months after the index diagnosis date. The study included patients' adult working family members who were eligible for absenteeism and who did not have any cancer diagnosis, and these family members were used as a proxy for caregivers. Productivity loss was measured as the leave days taken under the Family and Medical Leave Act (FMLA) or personal leave by the family members during a 12-month follow-up period. Associated indirect costs were estimated by multiplying leave days by daily wages obtained from the 2011 Bureau of Labor Statistics. A generalized linear model with a log link and gamma distribution was used.

The analysis included 209 family members of patients with MBC and 1,166 family members of patients with EBC who were eligible for absenteeism. The mean age was 50.5 years, and 1,373 caregivers (99.9%) were male. The main industries of employment of the family members were manufacturing (52%), transportation, communication, or utilities (28%), and oil and gas extraction or mining (15%). Compared with those of EBC patients, family members of MBC patients had more FMLA or personal leave days (mean 2.8 ± 6.1 days vs 2.1 ± 4.8 days, respectively; $P<.047$) and higher costs (mean \$2,366 ± \$5,095 vs \$1,741 ± \$3,995; $P<.047$). Similar proportions of family members had at least 1 FMLA or personal leave day (92 [44%] of the MBC arm vs 502 [43%] of the EBC arm). Mean absentee days for these family members were 6.4 ± 7.8 for the MBC arm versus 4.8 ± 6.3 for the EBC arm ($P=.033$). Mean costs were \$5,375 ± \$6,556 for the MBC arm versus \$4,043 ± \$5,272 for the EBC arm ($P=.033$). After adjusting for covariates, family members of MBC patients incurred 40% greater costs related to absenteeism due to FMLA or personal leave compared with family members of EBC patients ($P=.06$). Higher FMLA or personal leave costs were also associated with occupation in the oil and gas extraction or mining industries relative to the manufacturing non–durable goods industry ($P<.001$) and among the Northeast and South regions of the United States compared with the West ($P<.001$). The authors concluded that the higher productivity loss for family members of MBC patients is consistent with the differing goals, type, and length of treatment for MBC versus EBC patients.

S5-1 Biomarker Analyses in CLEOPATRA: A Phase III, Placebo-Controlled Study of Pertuzumab in HER2-Positive, First-Line Metastatic Breast Cancer (MBC)[30]

J Baselga, J Cortés, S-A Im, E Clark, A Kiermaier, G Ross, SM Swain

Collection of tumor tissue and serum samples was mandatory in the CLEOPATRA clinical study.[11] As part of this trial, an exploratory analysis was undertaken to identify subgroups based on biomarker profiles within the HER2-positive population with a differential benefit from HER2-targeted therapies.[30] A predefined panel of biomarkers was assessed in tumor tissue and serum samples to determine their predictive and prognostic values (Table 1).

The biomarkers were chosen to represent receptor kinases, ligands, and markers of key intracellular pathways. Correlations between biomarker expression levels and PFS were assessed, and a predictive value relating to pertuzumab treatment benefit was identified. The study also determined biomarker prognostic values by pooling PFS data from both treatment arms and relating the pooled data to biomarker expression levels. Median expression values were used as the cutoff point for high versus low biomarker expression levels, with 2 exceptions. High expression was defined as a target:centromere level of at least 2 for c-Myc, and for PIK3CA, 8 mutations (420R, 542K, 545K, 545A, 545G, 1047R, 1047L, and 1047Y) and 4 hotspots (in exons 7, 9, and 20) were used to identify wild-type versus mutant genes. Different sample sizes were analyzed for each biomarker as determined by

Table 1. Biomarkers Evaluated by Various Methods in the CLEOPATRA Trial

IHC*	qRT-PCR†	FISH	Mutational Analyses	ELISA (Serum Analyses)
HER2	HER2	c-Myc	PIK3CA (8 mutations, 4 hotspots)	sHER2
HER3	HER3			AREG
IGF-1 receptor	EGF receptor			EGF
PTEN	AREG			TGFα
pAKT	Betacellulin			

*By modified H-score.
†By concentration ratio.
AREG=amphiregulin; CLEOPATRA=Clinical Evaluation of Pertuzumab and Trastuzumab; EGF=epidermal growth factor; ELISA=enzyme-linked immunosorbent assay; FISH=fluorescence in situ hybridization; sHER=serum human epidermal growth factor receptor; IGF-1=insulin-like growth factor 1; IHC=immunohistochemistry; pAKT=phosphorylated Akt; qRT-PCR=quantitative reverse transcriptase polymerase chain reaction; TGFα=transforming growth factor alpha. Data from Baselga J et al. *N Engl J Med.* 2012;366:109-119.[11]

assay performance and by a predefined priority ranking. An exploratory subgroup analysis of PFS by biomarker expression level was conducted, with no attachments made for multiple testing.

No predictive value was discerned for any of the biomarkers evaluated, including serum levels of AREG, EGF, TGFα, and serum HER2 as determined by enzyme-linked immunosorbent assay (ELISA). Similarly, no ability to predict PFS benefit from pertuzumab treatment emerged from the immunohistochemistry (IHC) or quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) analysis of HER ligands and receptor tyrosine kinases in tumor tissue, including biomarkers AREG, EGFR, HER2, HER3, IGR1R, and betacellulin. Prognostic biomarker analysis suggested that low levels of serum HER2 correlated with improved disease outcome, but with borderline statistical significance (HR, 1.23; 95% CI, 1.01–1.49; *P*=.0433). Improved disease outcome regardless of treatment arm was observed for patients with higher expression levels of HER mRNA determined by qRT-PCR (HR, 0.77; 95% CI, 0.63–0.93; *P*=.0080) and for HER2 protein expression by IHC (HR, 0.83; 95% CI, 0.69–1.00; *P*=.0502). High levels of HER3 mRNA by qRT-PCR also correlated with improved outcome regardless of study treatment (HR, 0.81; 95% CI, 0.66–0.98; *P*=.0348). Among the intracellular pathway biomarkers, high levels of wild-type PIK3CA correlated with improved disease outcome (HR, 0.63; 95% CI, 0.49–0.80; *P*=.0001). A further exploratory analysis showed that patients with tumors harboring PIK3CA mutations had a worse outcome relative to patients with wild-type PIK3CA in the placebo arm (median PFS, 8.6 months vs 13.8 months, respectively) as well as in the pertuzumab treatment arm (median PFS, 12.5 months vs 21.8 months, respectively). However, a treatment benefit was observed from the addition of pertuzumab to trastuzumab and docetaxel for patients with wild-type or mutant PIK3CA: For patients with wild-type PIK3CA disease, median PFS improved from 13.8 months to 21.8 months (HR, 0.67; 95% CI, 0.50–0.89), and for patients with mutant PIK3CA, median PFS improved from 8.6 months to 12.5 months (HR, 0.64; 95% CI, 0.43–0.93). Thus patients with PIK3CA mutations may have a poorer prognosis and further unmet medical needs. The study identified 182 PIK3CA mutations overall, and the prognostic impact was not attributed to any single mutation or to the mutation of any single exon. An analysis of serum biomarker levels over time was also conducted and yielded no significant correlation with disease progression. The authors noted that the lack of a control arm of patients who did not receive HER2-targeted treatment may have prevented the identification of predictive biomarkers.

P5-20-04 Eribulin Mesylate + Trastuzumab as First-Line Therapy for Locally Recurrent or Metastatic HER2-Positive Breast Cancer: Results From a Phase 2, Multicenter, Single-Arm Study[31]

L Vahdat, L Schwartzberg, S Wilks, J Rege, S Zhou, D Cox, J O'Shaughnessy

A single-arm, multicenter, phase II study that has completed enrollment will evaluate the efficacy and safety of eribulin mesylate plus trastuzumab as first-line therapy for HER2-positive, locally recurrent or metastatic breast cancer.[31] Patients will receive eribulin mesylate (1.4 mg/m^2 on days 1 and 8) and trastuzumab (8 mg/kg loading dose followed by 6 mg/kg thereafter on day 1) in a 21-day cycle. Prior treatment with trastuzumab was allowed for enrollment; however, 12 months were required to have elapsed after any prior neoadjuvant or adjuvant chemotherapy. The primary endpoint is ORR, with secondary endpoints of safety, PFS, time to response, and DOR. Tumor assessments are performed based on RECIST 1.1 criteria every 6 weeks for the first 6 cycles and every 6–12 weeks thereafter.

Table 2. Best Tumor Responses in a Phase II Trial Evaluating Eribulin Mesylate Plus Trastuzumab

Response Category	Eribulin Plus Trastuzumab N=40
Objective Response Rate*	22 (55.0%)
95% CI	38.49–70.74
Complete Response	2 (5.0%)
Partial Response	20 (50.0%)
Stable Disease	15 (37.5%)
Progressive Disease†	1 (2.5%)
Not Evaluable/Unknown	2 (5.0%)
Clinical Benefit Rate‡	25 (62.5%)
95% CI	45.80–77.27
Disease Control Rate§	37 (92.5%)
95% CI	79.61–98.43

*Objective response rate includes complete response and partial response.
†In the patient with progressive disease, the diameter of the target lesion decreased, but a new bone lesion was seen.
‡Clinical benefit rate includes complete response, partial response, and stable disease (of at least 180 days in duration).
§Disease control rate includes complete response, partial response, and stable disease.
CI=confidence interval. Data from Vahdat L et al. Poster presented at the 2012 San Antonio Breast Cancer Symposium; December 4-8, 2012; San Antonio, TX. Poster P5-20-04.[31]

Data are presented for 40 of the 52 patients planned for enrollment who had received at least 1 dose of eribulin. Patients had a mean age of 58.1 years (range, 31–81 years). Metastases were present in the liver, lung, or bone in 52.5%, 42.5%, and 35.0% of patients, respectively. Forty percent of patients reported prior treatment with trastuzumab, mostly in the neoadjuvant or adjuvant setting, and 50.0% of patients reported prior taxane or anthracycline treatment. Patients had received a median 7.0 cycles (range, 0–24) of eribulin and a median 7.0 cycles (range, 1–25) of trastuzumab. The most common AEs were alopecia (82.5%), neutropenia (60.0%), fatigue (57.5%), peripheral neuropathy (47.5%), and nausea (45.0%); neutropenia (35.0%) was the most common grade 3/4 AE. Treatment-related serious AEs were documented in 4 study patients, including febrile neutropenia in 3 patients (7.5%), neutropenia in 2 patients (5.0%), and anemia, fatigue, and peripheral neuropathy each occurring in 1 patient (2.5%). Treatment-emergent AEs led to dose reductions, interruptions, or discontinuation in 20.0%, 22.5%, and 12.5% of patients, respectively. The ORR in this preliminary analysis is 55.0% (95% CI, 38.5–70.7), including 2 (5.0%) CRs and 20 (50.0%) PRs (Table 2). For the patients with a CR or PR, the median time to first response was 40 days (95% CI, 36–42 days). The median DOR was 204 days (95% CI, 141–541 days). The median PFS for the 40 treated patients was 9.2 months (95% CI, 6.70–19.06 months). The authors concluded that the combination of eribulin mesylate plus trastuzumab showed considerable activity with an acceptable toxicity profile in this patient setting.

P5-18-22 Long-Term Survival of Patients With HER2 Metastatic Breast Cancer Treated by Targeted Therapies[32]

F Fiteni, C Villanueva, L Chaigneau, L Cals, F Bazan, E Dobi, P Montcuquet, V Nerich, S Limat, X Pivot

A retrospective study of patients with HER2-positive MBC examined the characteristics of patients who survived 5 or more years after treatment.[32] The study used data from the Bonne Pratique de Chimiothérapie (BPC), a centralized medical database, to identify all patients with HER2-positive MBC treated from 2003 to 2010 in the 5 hospitals of the Franche-Comté region of France. For every line of anticancer treatment, the BPC records information regarding the place of treatment administration, the treating physician, dates of treatment cycles, regimen types, dose adjustments, treatment delays, and the cause of treatment interruption. The Franche-Comté cancer registry provided patient outcomes, as well as patient and tumor characteristics. OS was calculated from the date of first treatment for metastatic disease to the date of death or data cutoff. The study identified 217 patients with HER2-positive MBC, and these patients had a median OS of 45 months (95% CI, 37.0–48.9 months). Among these patients, 56 (26%) had survived longer than 5 years and had the following characteristics: median age at diagnosis was 55 years (range, 33–87 years), 20 patients (35.7%) had metastatic disease at presentation, and 20 patients (35.7%) had received adjuvant chemotherapy. The median DFI was 17 months. Metastases of the bone, liver, lung, or brain were reported in 23 (41%), 19 (34%), 13 (23%), and 4 (7%) patients, respectively. Thirty-nine patients (70%) had hormone receptor–positive tumors. One, 2, 3, or more lines of chemotherapy in the metastatic setting had been received by 16 (29%), 7 (12.5%), 7 (12.5%), and 26 (46%) patients, respectively. HER2-targeted therapy represented 79%, 61%, and 50% of first-, second-, and third-line treatments, respectively. All patients received trastuzumab or lapatinib treatment, and 18 patients (32%) were treated with an anthracycline-containing regimen. Seven of the patients demonstrated a CR, each of which was observed after 1 line of chemotherapy consisting of trastuzumab combined with a taxane. All 7 of these patients continued trastuzumab after achieving the CR, and all patients with hormone receptor–positive disease received hormonal therapy after the CR. Among the 56 patients identified as long-term survivors, 35 (62.5%) were still alive at the cutoff date of May 31, 2012.

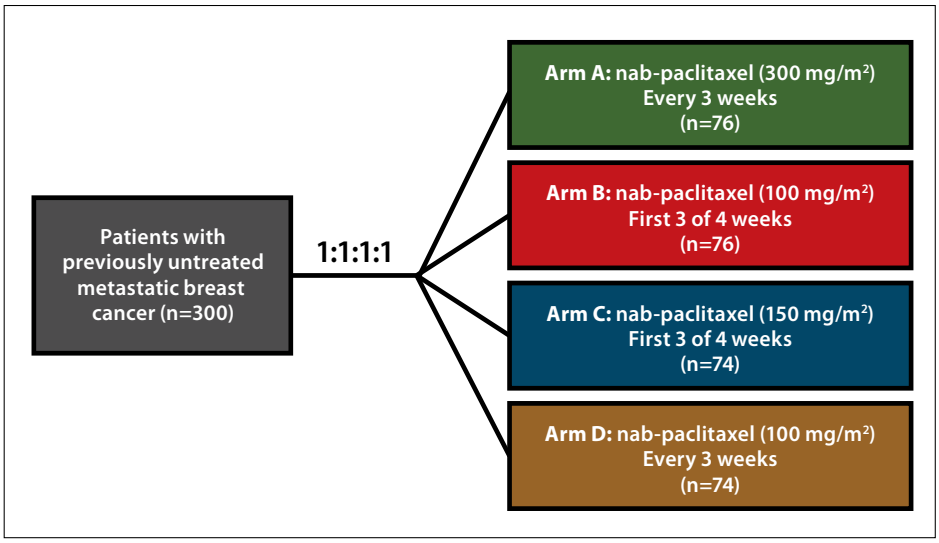

Figure 7. The study design of CA024, a phase II trial that randomized patients with metastatic breast cancer to receive first-line treatment of either weekly nab-paclitaxel at 1 of 3 doses and schedules or docetaxel every 3 weeks. Data from Gradishar WJ et al. *J Clin Oncol.* 2009;27:3611-3619.[39]

P1-12-07 A Retrospective Analysis of nab-Paclitaxel as First-Line Therapy for Metastatic Breast Cancer Patients With Poor Prognostic Factors[33]

J O'Shaughnessy, WJ Gradishar, P Bhar, J Iglesias

Visceral-dominant metastases and short DFI are predictive of poor outcomes in patients with MBC.[34-37] A phase III registration trial (CA012) randomized 454 MBC patients to receive either nab-paclitaxel (260 mg/m^2) or paclitaxel (175 mg/m^2) every 3 weeks as first-line or subsequent treatment and showed a higher ORR with nab-paclitaxel (33% vs 19%).[38] A phase II trial (CA024) randomized 300 MBC patients to receive first-line treatment of either weekly nab-paclitaxel at 1 of 3 doses and schedules or docetaxel every 3 weeks (Figure 7).[39] This trial also showed significantly higher ORRs and longer PFS compared with docetaxel. Based on the improved outcomes with nab-paclitaxel, a retrospective analysis was conducted to assess the safety and efficacy of first-line nab-paclitaxel in the patients in these 2 studies who had poor prognostic factors consisting of visceral-dominant metastases or DFI of 2 years or less.[33]

In the phase III trial, which included 186 first-line patients, nab-paclitaxel demonstrated a higher ORR in patients with visceral dominant metastases (42% vs 23%; *P*=.022) and in patients with early disease recurrence (43% vs 33%; *P*=not significant) compared with paclitaxel. In the phase II trial, higher ORRs were observed in patients with visceral dominant metastases for weekly nab-paclitaxel at 100 mg/m^2 (63%; *P*=.002) or at 150 mg/m^2 (75%; *P*<.001) for the first 3 weeks of each 4-week cycle versus docetaxel at 100 mg/m^2 every 3 weeks (37%). In patients with early disease recurrence, differences in ORR did not reach statistical significance for any of the nab-paclitaxel regimens relative to docetaxel.

In both trials, differences in PFS and OS for nab-paclitaxel treatment compared with control did not achieve statistical significance in either subgroup in most cases. However, a significant difference in PFS was observed in the phase II trial in patients with visceral dominant metastases in 2 cases. For patients in Arms B and C, who received weekly nab-paclitaxel for the first 3 weeks of the 4-week cycle, the higher dose of nab-paclitaxel resulted in a prolonged PFS (13.1 months vs 7.5 months; *P*=.010). In addition, weekly nab-paclitaxel (150 mg/m^2) for 3 out of 4 weeks was superior to docetaxel every 3 weeks (13.1 months vs 7.8 months; *P*=.019). Reported AEs in the 2 subgroups were similar to those for the intent-to-treat populations of both studies.

OT3-3-08 Eribulin/Cyclophosphamide Versus Docetaxel/Cyclophosphamide as Neoadjuvant Therapy in Locally Advanced HER2-Negative Breast Cancer: A Randomized Phase II Trial of the Sarah Cannon Research Institute[40]

DA Yardley, JD Hainsworth, M Shastry, L Finney, HA Burris

A phase II trial has been designed to evaluate 2 non-anthracycline combinations as neoadjuvant therapy in women with locally advanced, HER2-negative breast cancer.[40] In a phase III study of MBC patients previously treated with a taxane and an anthracycline, eribulin mesylate improved OS and was well tolerated.[2] In the neoadjuvant/adjuvant

setting, docetaxel plus cyclophosphamide improved disease-free survival (DFS) and OS compared with doxorubicin plus cyclophosphamide.[41] The primary objective of the current phase II study is to determine the partial CR (pCR) rate in patients with locally advanced, HER2-negative breast cancer treated with 6 cycles of neoadjuvant eribulin plus cyclophosphamide or docetaxel plus cyclophosphamide. Secondary objectives include evaluation of the toxicity profiles for both regimens, the clinical response rate of the eribulin combination as neoadjuvant therapy, and the 2-year DFS for both arms. Patient inclusion criteria include age of 18 years or older, HER2-negative status determined via FISH, colorimetric in situ hybridization, or IHC; histologically confirmed invasive adenocarcinoma of the breast with TNM (Tumor, Node, Metastasis) Classification of Malignant Tumours status of T1–T3, N0–N2, or M0; and ECOG PS of 0–2.

Initially, 10 patients will be treated with eribulin (1.4 mg/m^2 on days 1 and 8) plus cyclophosphamide (600 mg/m^2 on day 1) in a 21-day cycle to evaluate the safety and feasibility of the combination. If the safety of the combination is confirmed, another 66 patients will be enrolled and randomized in a 2:1 ratio to receive either eribulin/cyclophosphamide or docetaxel (75 mg/m^2 on day 1) plus cyclophosphamide (600 mg/m^2 on day 1) in a 21-day cycle.

After 3 treatment cycles have been completed, disease response will be evaluated via physical examination or breast imaging for nonpalpable lesions. Patients with evidence of stable disease or a response will continue treatment for a total of 6 cycles followed by surgical evaluation. Prophylactic growth factors are permitted after cycle 1. After completion of neoadjuvant chemotherapy, patients will receive definitive breast surgery, consisting of mastectomy or lumpectomy, and axillary node sampling or dissection based on physician and institutional standards. When possible, archival tumor samples will be collected at baseline and at surgery in patients with residual invasive breast cancer for potential exploratory biomarker analysis. Based on previous data with standard taxane-based therapy in this setting, a pCR rate of at least 18% in this study will be deemed sufficient for the eribulin/cyclophosphamide combination to merit further study.

S1-7 Phase III Trial Evaluating the Addition of Bevacizumab to Endocrine Therapy as First-Line Treatment for Advanced Breast Cancer - First Efficacy Results From the LEA Study[42]

M Martin, S Loibl, G von Minckwitz, S Morales, C Crespo, A Anton, A Guerrero, B Aktas, W Schoenegg, M Muñoz, JA Garcia-Saenz, M Gil, M Ramos, E Carrasco, C Liedtke, G Wachsmann, K Mehta, JR de la Haba

Preclinical and retrospective clinical data suggest that high levels of vascular endothelial growth factor (VEGF) in breast cancer specimens are associated with a reduced response to endocrine therapy.[43-46] The clinical efficacy of hormonal therapy may thus be improved by downregulating VEGF.[46] The combination of bevacizumab plus hormonal therapy has been explored in phase II trials, demonstrating the safety and activity of the combination.[47,48] Based on these findings, the phase III LEA (Letrozole/Fulvestrant and Avastin) study, conducted in Germany and Spain, was designed to examine whether adding anti-VEGF treatment to conventional hormonal therapy could delay the development of resistance to endocrine therapy in treatment-naïve patients.[42] The study enrolled 380 patients with unresectable, locally advanced or metastatic breast cancer that was hormone receptor–positive and HER2-negative. Patients were stratified based on prior treatment with adjuvant aromatase inhibitors (yes vs no), 1 lesion versus multiple lesions, measurable versus non-measurable lesions, and country (Spain vs Germany). Patients were randomized 1:1 to receive endocrine therapy alone—which consisted of single-agent letrozole (2.5 mg daily) or single-agent fulvestrant (250 mg every 28 days)—or combined therapy consisting of either hormone plus bevacizumab (15 mg/kg every 3 weeks). Treatment continued until disease progression. All patients had histologically confirmed, inoperable, locally advanced or metastatic breast cancer that was hormone receptor–positive and HER2-negative. The patients were postmenopausal, had an ECOG PS of 0 or 1, had adequate bone marrow reserve and organ function, and had received no previous therapy for advanced disease. Prior adjuvant treatment with an aromatase inhibitor was allowed. The study assumed an improvement in median PFS from 9 months with endocrine monotherapy, based on prior studies, to 13 months with the addition of bevacizumab. A total of 232 PFS events and 354 patients were required for 80% power and a 2-sided alpha level of 5%. A 2-sided log-rank test with a 5% significance level was used for comparisons of all time-to-event endpoints between treatment arms.

Enrolled patients had a median age of 63 years. Seventy percent of patients were enrolled in Spain and 30% in Germany. Nearly 50% of patients in both arms had received prior adjuvant chemotherapy, with most regimens consisting of taxane therapy, anthracycline therapy, or both. Approximately half of the patients had received prior adjuvant endocrine therapy, with most regimens consisting of antiestrogens, such as tamoxifen. Approximately 80% of patients had metastatic disease, and approximately 60% had multiple metastatic sites, with bone metastases present in 65% of patients. In both arms, 48% of patients had visceral disease. Approximately three-fourths of patients had measurable disease.

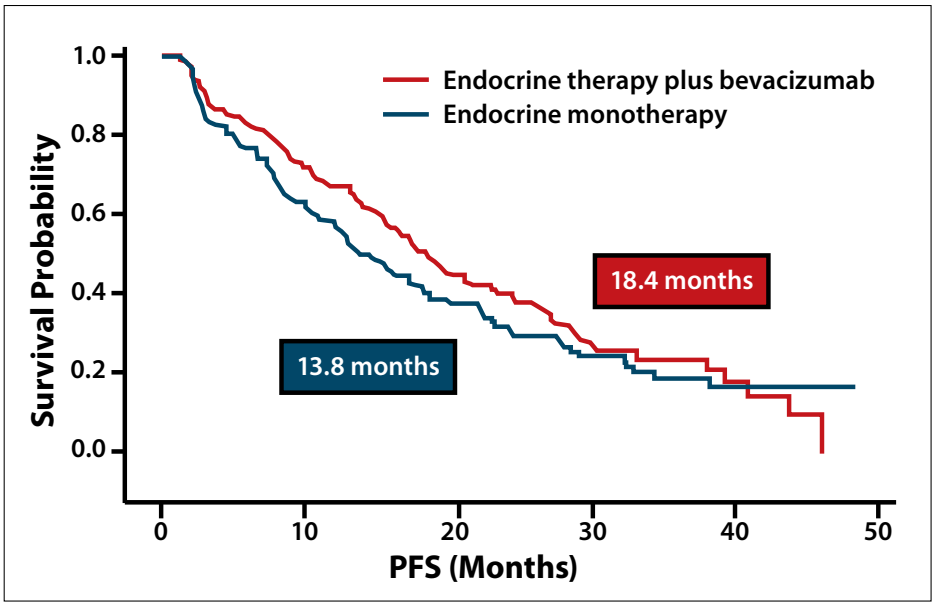

Figure 8. In the LEA trial, median PFS was 13.8 months for endocrine monotherapy versus 18.4 months for endocrine therapy plus bevacizumab, but the difference was not significant (HR, 0.83; 95% CI, 0.65–1.06; *P*=.14). LEA=Letrozole/Fulvestrant and Avastin; PFS=progression-free survival. Adapted from Martin M et al. Paper presented at the 2012 San Antonio Breast Cancer Symposium; December 4-8, 2012; San Antonio, TX. Abstract S1-7.[42]

Of the 189 patients randomized to receive endocrine therapy only, 89% received letrozole and 11% received fulvestrant. Of the 191 patients who received combination treatment, 92% received letrozole and 8% received fulvestrant. Detailed toxicity data were presented previously.[49] No important hematologic safety issues were raised, although the frequency of any-grade leukopenia was higher in patients who received bevacizumab (24.6% vs 11.4%; *P*=.001) and thrombocytopenia (19.3% vs 9.1%; *P*=.006). Among nonhematologic AEs of any grade, bevacizumab was associated with increased rates of fatigue (50.5% vs 29.0%; *P*<.001), hypertension (59.0% vs 15.9%; *P*<.001), hemorrhage (18.6% vs 1.7%; *P*<.001), liver enzyme elevation (46.5% vs 28.0%; *P*<.001), and proteinuria (30.3% vs 2.8%; *P*<.001). The only reported increase in grade 3/4 events with bevacizumab was for hypertension (3.2% vs 0%; *P*<.030). Median PFS was 13.8 months for endocrine monotherapy versus 18.4 months with the addition of bevacizumab, but the difference was not significant (HR, 0.83; 95% CI, 0.65–1.06; *P*=.14; Figure 8). The study recorded a total of 131 PFS events in the monotherapy arm and 117 PFS events in the combination arm. The latter included 7 patients who died during treatment, and some of the deaths were considered likely to be treatment-related. Overall survival was also similar between the 2 arms (*P*=.4589). The authors noted that the PFS and OS results for the control arm were generally higher than anticipated during study design and may have contributed to the failure to discern a significant difference in treatment outcomes between the 2 arms.

P5-18-01 Pertuzumab (P) in Combination With Trastuzumab (T) and Docetaxel (D) in Elderly Patients With HER2-Positive Metastatic Breast Cancer in the CLEOPATRA Study[50]

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Cancer patients aged 65 years or older are underrepresented in treatment trials, and older breast cancer patients may be undertreated.[51,52] The randomized, double-blind, placebo-controlled, phase III CLEOPATRA trial showed the increased efficacy of adding pertuzumab to trastuzumab plus docetaxel and led to the approval of the pertuzumab combination for HER2-positive, first-line MBC in June 2012.[11] The current analysis compared the efficacy and safety of patients younger than 65 years versus 65 years or older treated in CLEOPATRA with the aim of determining the benefit-risk ratio for pertuzumab plus trastuzumab and docetaxel in older patients.[50] In the intent-to-treat population of patients younger than 65 years, independently assessed median PFS was higher in the pertuzumab treatment arm compared with placebo (17.2 months vs 12.5 months; HR, 0.65; 95% CI, 0.53–0.80; *P*<.0001). In patients ages 65 years or older, independently assessed median PFS was also extended with pertuzumab combination treatment relative to placebo (21.6 months vs 10.4 months; HR, 0.52; 95% CI, 0.31–0.86; *P*=.0098). In both treatment arms, patients younger

than 65 years received a median 8.0 cycles of docetaxel. The older patients received fewer cycles of docetaxel: a median of 6.5 cycles in the placebo arm and 6.0 cycles in the pertuzumab arm. Dose reductions to less than 75 mg/m^2 of docetaxel occurred more often in patients ages 65 years or older. The older patients had higher rates of diarrhea, fatigue, asthenia, decreased appetite, vomiting, and dysgeusia in both treatment arms as compared with the younger patients. Among younger patients, diarrhea of at least grade 3 was reported in 4.8% in the placebo arm and 6.6% of patients in the pertuzumab arms. The rates among the older population were 6.2% in the placebo arm and 14.8% in the pertuzumab arm. Neutropenia and febrile neutropenia were less frequent in the patients ages 65 years or older, which the authors inferred was likely due to the reduced exposure to docetaxel. The authors concluded that, based on the AE profile observed in CLEOPATRA, use of the combination of pertuzumab, trastuzumab, and docetaxel should not be limited by age in patients with good performance status.

P1-12-01 Evaluation on Efficacy and Safety of Capecitabine Plus Docetaxel Versus Docetaxel Monotherapy in Metastatic Breast Cancer Patients Pretreated With Anthracycline: Results From a Randomized Phase III Study (JO21095)[53]

N Sato, D Yamamoto, Y Rai, H Iwase, M Saito, H Iwata, N Masuda, S Oura, J Watanabe, K Kuroi

A large phase III study demonstrated that the addition of capecitabine to docetaxel improved PFS and OS in patients with MBC.[54,55] However, the combination increased the frequency of grade 3/4 events and led to more frequent dose reductions relative to docetaxel monotherapy. A phase Ib study was therefore designed to determine the optimal dose of docetaxel plus capecitabine in Japanese patients with MBC and produced a recommended regimen of capecitabine (1,650 mg/m^2/day on days 1–14) plus docetaxel (60 mg/m^2 or 70 mg/m^2 on day 1) in a 3-week cycle.[56] Based on these findings, a randomized phase III study was designed to examine the efficacy and tolerability of low-dose docetaxel/capecitabine versus docetaxel monotherapy in Japanese patients with HER2-negative MBC previously treated with an anthracycline.[53] A measurable tumor and ECOG PS of 0 or 1 were also required. Patients were randomized to receive either concurrent docetaxel (60 mg/m^2 on day 1) plus capecitabine (1,650 mg/m^2 on days 1–14) every 3 weeks (n=82) or sequential docetaxel (70 mg/m^2 every 3 weeks), administered until disease progression, followed by capecitabine (2,500 mg/m^2 on days 1–14) every 3 weeks (n=81).

The analyses compared results from patients who received concurrent docetaxel plus capecitabine versus patients who had received docetaxel only in the sequential therapy arm. The primary endpoint of median PFS was 10.5 months with concurrent treatment versus 9.8 months for docetaxel monotherapy (HR, 0.62; 95% CI, 0.40–0.97; *P*=.0342). Results were also superior in the concurrent treatment arm versus the docetaxel monotherapy arm based on ORR (70% vs 61%, respectively) and time to treatment failure (9.6 months vs 7.0 months, respectively). Median OS had not been reached. Subgroup analyses revealed a significant improvement in PFS for patients with liver metastasis (HR, 0.39; 95% CI, 0.19–0.84) and in patients with lung metastasis (HR, 0.43; 95% CI, 0.21–0.90) for concurrent docetaxel plus capecitabine compared with docetaxel only. Treatment-related AEs were reported in 74.4% of patients receiving concurrent treatment and in 76.3% of patients in the sequential treatment arm. The most common treatment-related AEs of grade 3 or greater in patients receiving concurrent docetaxel plus capecitabine versus docetaxel monotherapy included decreased neutrophil count (57.3% vs 60.0%, respectively), neutropenia (8.5% vs 12.5%, respectively), and febrile neutropenia (6.1% vs 10.0%, respectively). Treatment-related AEs that occurred with at least a 5% difference between the combination and monotherapy arms included hand-foot syndrome (7.3% vs 0%, respectively), fatigue (2.4% vs 8.8%, respectively), and peripheral edema (1.2% vs 6.3%, respectively).

P1-12-05 First-Line Chemotherapy With Pegylated Liposomal Doxorubicin Versus Capecitabine in Elderly Patients With Metastatic Breast Cancer: Results of the Phase III OMEGA Study of the Dutch Breast Cancer Trialists' Group (BOOG)[57]

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Elderly patients with MBC remain under-represented in clinical trials; therefore, information on the efficacy and safety of chemotherapy in elderly patients is limited, particularly for patients ages 75 years or older.[58-60] Therefore, an open-label, multicenter, phase III study was undertaken to evaluate treatment efficacy and toxicity in elderly patients and to relate toxicity to the number of geriatric conditions.[57] MBC patients ages 65 years or older were randomized to liposomal doxorubicin (45 mg/m^2 every 4 weeks on day 1) or capecitabine (1,000 mg/m^2 twice daily

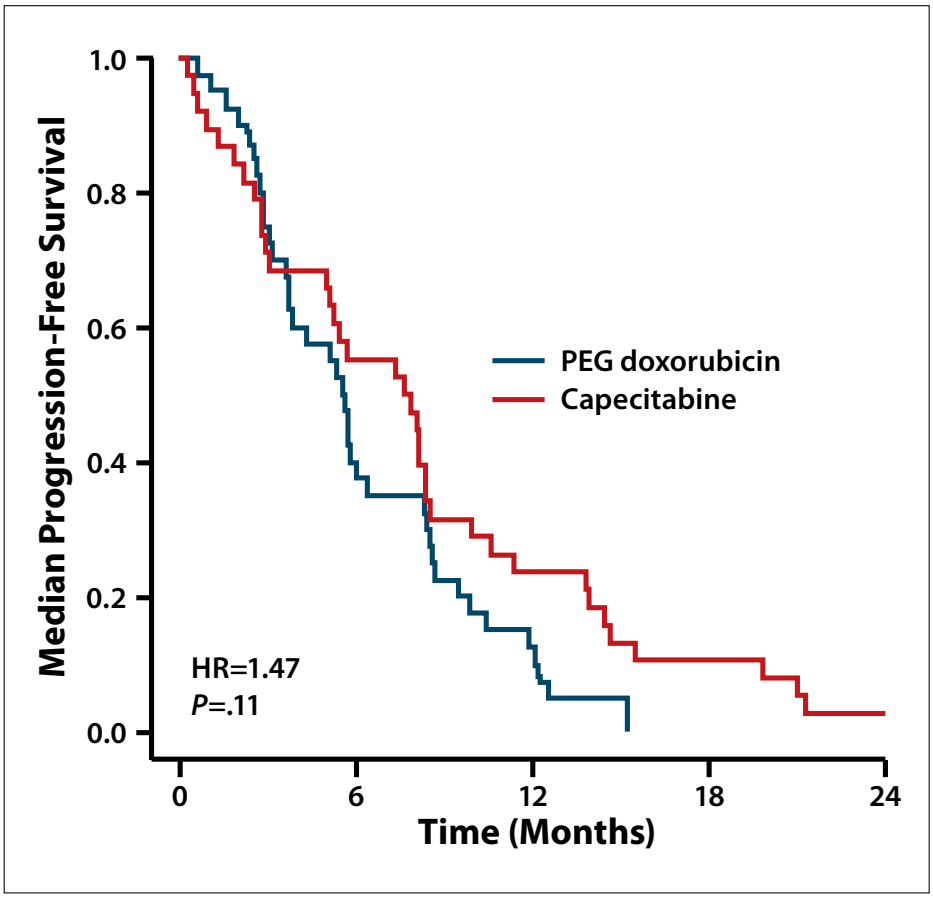

Figure 9. In the phase III OMEGA Study of the Dutch Breast Cancer Trialists' Group, the median progression-free survival was 5.6 months for pegylated (PEG) doxorubicin versus 7.7 months for capecitabine. Adapted from Smorenburg CH et al. Poster presented at the 2012 San Antonio Breast Cancer Symposium; December 4-8, 2012; San Antonio, TX. Poster P1-12-05.[57]

on days 1–14 every 3 weeks) for 24 weeks as first-line treatment. Eligibility criteria included an ECOG PS of 0–2, but patients with an ECOG PS of 3 were allowed if the status was due to pain or preexisting comorbidity. Patients were stratified based on ECOG PS (0 or 1 vs 2 or 3), HER2 status, visceral versus non-visceral disease, adjuvant hormonal therapy, and hormonal therapy as treatment for MBC. The study endpoints were to compare PFS, ORR, OS, toxicity, and compliance for each treatment, and to evaluate the relationship between comprehensive geriatric assessment (CGA) and toxicity. The study had a planned sample size of 154 patients, with a planned interim analysis of 77 patients. However, the study was closed prematurely after enrolling 78 patients due to slow patient accrual and difficulty in obtaining pegylated doxorubicin.

The patients' mean age was 74 years (range, 65–86 years), with patients ages 75 years or older comprising 48% of the pegylated doxorubicin arm and 61% of the capecitabine arm. Out of 75 patients with baseline CGA, 32 (43%) had 1 geriatric condition and 21 (28%) had 2 or more geriatric conditions. Thirty-eight percent of patients received chemotherapy for 6 months, and the mean dose intensity was 84–85% in both arms. Reasons for early treatment discontinuation in the pegylated doxorubicin arm versus the capecitabine arm included progressive disease (38% vs 26%, respectively), toxicity (22% vs 21%, respectively), and intercurrent death (2% vs 8%, respectively). The median PFS was 5.6 months for pegylated doxorubicin versus 7.7 months for capecitabine (HR, 1.47; *P*=.11; Figure 9). The median OS was 13.8 months for pegylated doxorubicin versus 16.8 months for capecitabine (HR, 1.69; *P*=.59). Patients older than 75 years had a 2-fold increased risk of dying irrespective of the treatment arm relative to younger patients (HR, 1.98; *P*=.02). ORRs were comparable for both treatments, and included 18% versus 16% PRs and 45% versus 52% SD for pegylated doxorubicin versus capecitabine, respectively. Toxicity was acceptable and consisted mainly of grade 1–2 events. The most common grade 3/4 events were hand-foot syndrome (11–15%) and fatigue (13%). Incidence of grade 3/4 toxicity was significantly related to the number of geriatric conditions in the capecitabine arm (*P*=.002).

P5-20-06 RAD001 (Everolimus) in Combination With Letrozole in the Treatment of Postmenopausal Women With Estrogen Receptor Positive Metastatic Breast Cancer After Failure of Hormonal Therapy—A Phase II Study[61]

T Safra, J Greenberg, L Rivo, B Kaufman, E Evron, N Ben Baruch, L Kadouri-Sonenfeld, B Nisenbaum, R Yerushalmi

An open-label, multicenter, phase II study evaluated treatment with everolimus (10 mg daily) plus letrozole (2.5 mg daily) in postmenopausal women with hormone receptor–positive MBC after recurrence or progression on 1 or more of the following drugs: tamoxifen, anastrozole, letrozole, fulvestrant, and exemestane.[61] The primary objective was ORR, with secondary objectives of PFS, OS, and safety. The study enrolled 69 patients in 7 institutions in Israel. Preliminary findings were presented based on a median follow-up of 8.1 months in 62 evaluable patients. Median age was 54 years (range, 32–80 years). Sixty patients (87%) had bone metastasis and 32 (46%) had visceral metastasis. Patients had received a median 2 previous lines (range, 1–5 lines) of hormonal therapy for advanced breast cancer, and 26 patients (37.7%) had received letrozole. The ORR was 17.7% (11 of 62 patients), and the clinical benefit rate was 75.8% (47 of 62 patients). PFS was 8.7 months (range, 6.4–10.3 months). Multivariate Cox regression analysis showed that PFS was not affected by the number of previous lines of hormonal therapy (P=.25), previous letrozole failure (P=.32), or visceral versus bone or nodal disease (P=.29). The most frequently observed toxicities of any grade, occurring in at least 20% of patients, were stomatitis (52%), weakness (47%), weight loss (42%), hyperlipidemia (29%), myalgia/arthralgia (29%), anemia (27%), and anorexia (26%). The authors concluded that the preliminary results were consistent with findings from the BOLERO-2 study, which showed a significant prolongation of PFS when everolimus was added to an aromatase inhibitor in postmenopausal patients with advanced breast cancer who failed previous endocrine therapy.[16]

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Commentary

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Presentations at the 2012 San Antonio Breast Cancer Symposium (SABCS) offered important new data on the management of metastatic breast cancer. Clinical trials examined therapies such as eribulin mesylate, capecitabine, bevacizumab, pertuzumab, everolimus, and the novel agent PD 0332991.

I presented results from a phase III randomized trial of eribulin mesylate versus capecitabine in women with locally advanced or metastatic breast cancer who had previously been treated with an anthracycline and a taxane in either the adjuvant or neoadjuvant setting.[1] Eribulin was approved by the US Food and Drug Administration (FDA) in 2010 for the treatment of patients with metastatic breast cancer who have previously received an anthracycline and a taxane in either the adjuvant or metastatic setting, and at least 2 chemotherapeutic regimens for the treatment of metastatic disease.[2] The FDA approval was based on results of the phase III EMBRACE (Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389) trial,[3] which demonstrated a survival benefit, a rare and impressive finding in metastatic breast cancer. Eribulin is a non-taxane, microtubule dynamics inhibitor that is a synthetic analogue of halichondrin B. As shown in previous studies, the adverse event profile of eribulin is manageable and includes grade 3/4 neuropathy and neutropenia.[3] The neutropenia is not associated with fever, a clinically meaningful finding.

There has been interest in examining eribulin earlier in the course of metastatic breast cancer as a consequence of the data from the EMBRACE trial. Our study presented at the 2012 SABCS included women with metastatic breast cancer in the first-line, second-line, and third-line treatment settings.[1] Approximately 20% of patients were in the first-line setting; they had received no prior cytotoxic chemotherapy regimens in the setting of metastatic disease. (They may have received hormonal therapy or biologics.) Approximately 50% of women were in the second-line setting. The take-home message of the study was that it showed a small numerical trend favoring eribulin over capecitabine in regard to overall survival, although the difference was not statistically significant. We were hoping to demonstrate that eribulin was associated with a statistically significant benefit, but that was not seen. Overall, however, eribulin demonstrated results that were comparable to capecitabine. My coauthors and I concluded that this study demonstrates activity of eribulin in the first-line, second-line, and third-line settings, and that eribulin is a reasonable therapeutic option for these patients. Several preplanned subset analyses of our study revealed interesting trends regarding overall response rates that did not reach statistical significance. Trends favored eribulin over capecitabine in patients with triple-negative breast cancer, estrogen receptor (ER)-negative disease, and human epidermal growth factor receptor 2 (HER2)-negative disease. Among patients in these subgroups, eribulin was associated with improved hazard ratios compared to capecitabine. The adverse events were as expected and consistent with data in prior studies. Overall, we thought that the study findings were interesting and important. Further subset analyses are planned, and a formal analysis of quality of life data is under way.

Several more studies on eribulin were presented at the 2012 SABCS. Dr. Linda Vahdat presented data from a single-arm, phase II trial evaluating eribulin in combination with trastuzumab as first-line treatment in the setting of HER2-positive metastatic breast cancer.[4] These data are the first looking at eribulin in combination with trastuzumab, an area in which there has been much interest. The findings were promising for a phase II study. There was an impressive level of therapeutic activity. The response rate was approximately 55%, which is consistent with other cytotoxic agents, such as taxanes, in combination with trastuzumab in the first-line, HER2-positive setting. The time to disease progression and progression-free survival were also consistent with previous data. No unusual adverse events were seen.

A phase II, single-arm trial examined eribulin as first-line therapy for locally recurrent or metastatic HER2-negative breast cancer.[5] The response rate was 27%, and the adverse events were manageable. This study confirms that eribulin has activity and is comparable to other cytotoxic agents in the first-line setting for metastatic breast cancer.

The current standard of care in patients with ER-positive metastatic breast cancer is hormonal therapy. The LEA (Letrozole/Fulvestrant and Avastin) trial provided the first phase III data regarding bevacizumab in combination with hormonal therapy in these patients.[6] This randomized trial evaluated hormonal therapy alone versus hormonal therapy plus bevacizumab as first-line treatment (with hormonal therapy) for patients with ER-positive metastatic breast cancer. The design allowed the hormonal therapy to be either letrozole or fulvestrant

based on the treating oncologist's choice. Patients were then randomized to receive or not receive bevacizumab. The study found no statistically significant improvement with the addition of bevacizumab. There was, however, a nonsignificant trend that favored bevacizumab: the median progression-free survival was 18.4 months in the patients who received bevacizumab and 13.8 months in the patients who did not receive bevacizumab. Overall survival data were also reported, but they were premature. The authors concluded that it was not possible to rule out a small beneficial impact for bevacizumab that the study was unable to capture. The authors are proceeding with a biomarker analysis to identify any subsets of patients who might benefit from the use of bevacizumab, a goal shared by several teams of investigators.[7-9]

CLEOPATRA (Clinical Evaluation of Pertuzumab and Trastuzumab) is a large, phase III randomized trial of pertuzumab in patients with HER2-positive metastatic disease. Initial data were presented at the 2011 SABCS and showed a statistically significant difference in progression-free survival, but not in overall survival.[10] A presentation at the 2012 SABCS demonstrated a statistically significant benefit in overall survival.[11] These data substantiate the use of pertuzumab in patients with HER2-positive metastatic breast cancer who are in the first-line setting (referring to chemotherapy). These data confirm that the previous standard of care consisting of a taxane and trastuzumab is improved with the addition of pertuzumab. Importantly, this updated analysis yielded no additional safety signals, including no increase in cardiotoxicity, an important quality in HER2-targeted therapies. Overall, pertuzumab has an acceptable side effect profile.

Final data from the BOLERO-2 (Breast Cancer Trials of Oral Everolimus) trial were presented.[12] Previous data from this study demonstrated a very substantial, statistically significant, and clinically meaningful impact of everolimus when added to hormonal therapy.[13] These data were widely viewed as impressive. The 2012 presentation showed that progression-free survival was 4.1 months for patients receiving placebo versus 11.0 months for patients receiving everolimus. A preliminary analysis of overall survival after 200 deaths used immature data, but it showed no significant difference between the 2 treatment arms (25.4% with placebo vs 32.2% with everolimus).

A phase II trial of the novel cyclin-dependent kinase (CDK) inhibitor PD 0332991 in combination with hormonal therapy in patients with ER-positive metastatic disease received much attention.[14] It compared hormonal therapy alone versus hormonal therapy plus the novel CDK inhibitor. The results showed an impressive benefit for PD 0332991. The overall response rate was 34% for PD 0332991 plus letrozole versus 26% with letrozole alone. Among patients with measurable disease, the addition of PD 0332991 improved the clinical benefit rate (44% with letrozole alone vs 70% with the combination) and progression-free survival (7.5 months with letrozole alone vs 26.1 months with the combination).

Acknowledgment

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

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Highlights in Metastatic Breast Cancer From the 2012 San Antonio Breast Cancer Symposium (SABCS)

CME Post-Test: *Circle the correct answer for each question below.*

1. In a phase III trial by Kaufman and colleagues comparing eribulin mesylate and capecitabine, progression-free survival was ___ in both arms.

   a. 3.1–3.2 months
   b. 3.7—3.8 months
   c. 4.1–4.2 months
   d. 4.7–4.8 months

2. In the second interim analysis of the CLEOPATRA trial, what was the investigator-assessed progression-free survival associated with pertuzumab?

   a. 12.5 months
   b. 13.8 months
   c. 15.6 months
   d. 18.7 months

3. In the final progression-free survival analysis of the BOLERO-2 trial, analysis by local radiologic assessment showed a risk reduction of ____ for patients receiving everolimus relative to placebo.

   a. 50%
   b. 55%
   c. 60%
   d. 65%

4. Which of the following is the only chemotherapeutic agent with a proven survival benefit for patients with heavily pretreated metastatic breast cancer?

   a. Capecitabine
   b. Eribulin mesylate
   c. Nab-paclitaxel
   d. Pertuzumab

5. In a phase II study of PD 0332991 in combination with letrozole versus letrozole alone, the clinical benefit rate improved with the addition of PD 0332991 from ____.

   a. 23% to 41%
   b. 37% to 63%
   c. 44% to 70%
   d. 51% to 82%

6. In a retrospective study assessing family members' burden in patients with metastatic or early stage breast cancer, costs related to absenteeism were ____ higher in family members of patients with metastatic breast cancer.

   a. 25%
   b. 30%
   c. 35%
   d. 40%

7. In a retrospective study by Fiteni and colleagues of targeted therapies, what was the median disease-free interval?

   a. 13 months
   b. 15 months
   c. 17 months
   d. 19 months

8. In first efficacy results from the LEA study, median progression-free survival was ____ for endocrine monotherapy.

   a. 12.5 months
   b. 13.8 months
   c. 15.6 months
   d. 18.7 months

9. The final planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831 showed an improvement of ____ in overall survival for patients who received trastuzumab compared with paclitaxel.

   a. 5.5%
   b. 6.6%
   c. 7.7%
   d. 8.8%

10. In a phase II study testing the efficacy and safety of carboplatin plus nab-paclitaxel plus bevacizumab, what was the overall response rate?

    a. 40%
    b. 50%
    c. 60%
    d. 70%

Project ID: 9235

Evaluation Form: Highlights in Metastatic Breast Cancer From the 2012 San Antonio Breast Cancer Symposium (SABCS)

PIM is committed to excellence in continuing education, and your opinions are critical to us in this effort. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment for completing this activity.

Please rate your level of agreement by circling the appropriate rating:
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

Learning Objectives
After participating in this activity, I am now better able to:

1. Discuss efficacy and safety data from new and emerging agents for the treatment of metastatic breast cancer	1 2 3 4 5
2. Recognize patient characteristics that help determine management strategies	1 2 3 4 5
3. Incorporate newly approved agents into treatment regimens to improve response and survival outcomes of metastatic breast cancer patients	1 2 3 4 5
4. Identify future research directions and novel targets in the treatment of metastatic breast cancer	1 2 3 4 5

Based upon your participation in this activity, choose the statement(s) that apply:
❒ I gained new strategies/skills/information that I can apply to my area of practice.
❒ I plan to implement new strategies/skills/information into my practice.
❒ I need more information before I can implement new strategies/skills/information into my practice behavior.
❒ This activity will not change my practice, as my current practice is consistent with the information presented.
❒ This activity will not change my practice, as I do not agree with the information presented.

What strategies/changes do you plan to implement into your practice? _____

_____

How confident are you that you will be able to make this change?
❒ Very confident ❒ Unsure
❒ Somewhat confident ❒ Not very confident

What barriers do you see to making a change in your practice? _____

_____

Please rate your level of agreement by circling the appropriate rating:
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

The content presented:

Enhanced my current knowledge base	1 2 3 4 5
Addressed my most pressing questions	1 2 3 4 5
Promoted improvements or quality in health care	1 2 3 4 5
Was scientifically rigorous and evidence-based	1 2 3 4 5
Avoided commercial bias or influence	1 2 3 4 5
Provided appropriate and effective opportunities for active learning (e.g., case studies, discussion, Q&A, etc)	1 2 3 4 5
My opportunity for learning assessment was appropriate to the activity	1 2 3 4 5

Handout materials were useful: ❒ Yes ❒ No ❒ No handouts for this activity

Would you be willing to participate in a post-activity follow-up survey? ❒ Yes ❒ No

Please list any clinical issues/problems within your scope of practice you would like to see addressed in future educational activities:

_____

If you wish to receive acknowledgment for completing this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876. You may also complete the post-test online at www.cmeuniversity.com. On the navigation menu, click on "Find Post-tests by Course" and search by **project ID 9235**. Upon successfully registering/logging in, completing the post-test and evaluation, your certificate will be made available immediately.

Post-test Answer Key

1	2	3	4	5	6	7	8	9	10

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For Physicians Only: I certify my actual time spent to complete this educational activity to be:
❒ I participated in the entire activity and claim 1.5 credits.
❒ I participated in only part of the activity and claim _____ credits.