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Highlights in Metastatic Breast Cancer From the 2013 San Antonio Breast Cancer Symposium (SABCS)

A Review of Selected Presentations From the
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Symposium (SABCS)
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Target Audience

This activity has been designed for all physicians, academicians, researchers, investigators, support staff, nurses, and program directors from the fields of oncology with a special interest in metastatic breast cancer.

Statement of Need/Program Overview

Treatment of women with metastatic breast cancer lacks a single standard of care. Several novel agents have been approved in the past 5 years, and others are undergoing evaluation in clinical trials. The management of symptoms in women with metastatic breast cancer can be complicated by the additive effects of treatment toxicity. Personalized management, based on factors such as hormone receptor and human epidermal growth factor receptor 2 status, previous therapies, tumor burden, patient age, and comorbidities can improve outcomes. A large proportion of the abstracts presented at the 2013 San Antonio Breast Cancer Symposium focused on metastatic disease. Clinical trials of novel agents and regimens offered both positive and negative data. Cellular studies provided insight into the mechanism of the disease and identified potential avenues for treatment.

Educational Objectives

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

- Evaluate efficacy and safety data for new and emerging agents for the treatment of metastatic breast cancer
- Incorporate newly approved agents into treatment regimens to improve response and survival outcomes of metastatic breast cancer patients
- Implement individualized management plans based on factors such as hormone receptor and human epidermal growth factor receptor 2 status, previous therapies, tumor burden, patient age, and comorbidities
- Discuss future research directions and novel targets in the treatment of metastatic breast cancer

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Highlights in Metastatic Breast Cancer From the 2013 San Antonio Breast Cancer Symposium (SABCS)

P3-14-14 Neoadjuvant Phase II Trial With Carboplatin and Eribulin in Triple Negative Breast Cancer Patients[1]

SB Giordano, JS Jeruss, KP Bethke, NM Hansen, S Khan, J Von Roenn, S Rosen, WL Gradishar, KP Siziopikou, C Meservey, V Kaklamani

A phase 2 neoadjuvant trial by Dr Sara Giordano and colleagues enrolled 30 patients with biopsy-confirmed breast cancer at stages I through III who were negative for the estrogen receptor (ER), the progesterone receptor, and the human epidermal growth factor receptor 2 (HER2).[1] These triple-negative patients received four 3-week cycles of carboplatin at a dose of an area under the curve of 6 on day 1 and eribulin at either 1.4 mg/m^2 or 1.1 mg/m^2 on days 1 and 8. The median age of the patients was 52.5 years.

The pathologic complete response rate was 43.3% (n=13; 95% CI, 0.25-0.61). Clinical responses included 5 patients (17.2%) with stable disease, 17 patients (58.6%) with a partial response, and 7 patients (24.2%) with a complete response. The clinical response rate (partial response plus complete response) was 80% (24 patients).

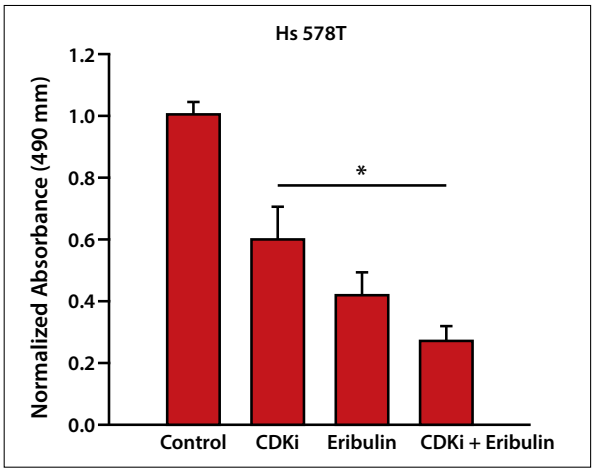

Figure 1. A phase 2 trial in patients with triple-negative breast cancer showed increased synergistic effects when a cyclin-dependent kinase inhibitor (CDKi) was combined with eribulin compared with either treatment alone. *Differences were statistically significant from other groups.

Adapted from Giordano SB et al. Abstract P3-14-14. Poster presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX.[1]

Hematologic adverse events (AEs) included leukopenia in 16 patients (6 with grade 3), neutropenia in 22 patients (12 with grade 3 and 5 with grade 4), anemia in 29 patients (6 with grade 3), and thrombocytopenia in 24 patients (5 with grade 3 and 1 with grade 4.) Nonhematologic AEs included fatigue, nausea, constipation, elevated aspartate aminotransferase (AST), elevated alanine aminotransferase (ALT), increased creatinine, and alopecia. The only grade 3 nonhematologic AE—elevated ALT—occurred in 1 patient, and no grade 4 nonhematologic AEs were observed.

Cell culture studies indicated synergistic effects from combining a cyclin-dependent kinase inhibitor and eribulin compared with either treatment alone (Figure 1). The authors suggested that the combination of eribulin with carboplatin and a cyclin-dependent kinase inhibitor in patients with triple-negative breast cancer (TNBC) should be a focus of future trials.

S3-07 Letrozole Plus Dasatinib Improves Progression-Free Survival (PFS) in Hormone Receptor-Positive, HER2-Negative Postmenopausal Metastatic Breast Cancer (MBC) Patients Receiving First-Line Aromatase Inhibitor (AI) Therapy[2]

D Paul, SJ Vukelja, FA Holmes, J Blum, KJ McIntyre, AR Kumar, DL Lindquist, CR Osborne, IJ Sanchez, JH Goldschmidt, Y Wang, L Asmar, ME Lee, N Wu, K Logie, J O'Shaughnessy

The protein c-Src is a pleomorphic, nonreceptor tyrosine kinase that is involved in the invasion, proliferation, and survival of breast cancer.[3] Membrane ER-α forms complexes with c-Src and phosphoinositide 3-kinase (*PI3K*) to drive the growth of breast cancer and its resistance to endocrine therapy.[4,5] Also, c-Src regulates osteoclast-mediated turnover of bone, and it is known to be important in enabling crosstalk between the ER and the HER2 family and with other steroid hormone receptors. Combined inhibition of aromatase and c-Src has greater breast cancer antitumor activity than either strategy alone.[6] The androgen receptor is one of the receptors of c-Src, and it leads to activation of the mitogen-activated protein kinase and *PI3K* pathways. Ultimately, this activation affects

transcription, DNA synthesis, and the proliferation and survival of breast cancer cells.

Dasatinib is an oral adenosine triphosphate–competitive inhibitor of 5 tyrosine kinase families: c-Src, BCR-ABL, c-KIT, platelet-derived growth factor-β, and ephrin kinases. Dasatinib is approved by the US Food and Drug Administration (FDA) to treat chronic myelogenous leukemia. An oral 100-mg pill of dasatinib taken daily is safe and effective in chronic myelogenous leukemia.[7] Combining tamoxifen and dasatinib inhibits the in vivo growth of breast cancers that are resistant to endocrine therapy.[4] The effects of dasatinib on bone are both anabolic and antiresorptive.[8]

The hypothesis for a study by Dr Devshand Paul and coworkers was that combining letrozole with dasatinib as first-line aromatase inhibitor treatment for metastatic breast cancer would improve the clinical benefit rate and progression-free survival (PFS) compared with letrozole alone.[2] The primary endpoint of the study was the clinical benefit rate, defined as the rates of complete response, partial response, and stable disease of at least 6 months. Secondary objectives included PFS, objective response rate, toxicity, and changes in bone mineral density. This phase 2, noncomparative, parallel-group study enrolled 120 patients in a 1-to-1 randomization. Patients were stratified by a disease-free interval of 2 years or less vs a disease-free interval of longer than 2 years, and by prior tamoxifen use vs no prior tamoxifen.

The final analysis of the study was performed in October 2013, after all the patients had become evaluable for the primary endpoint of clinical benefit. The enrolled women were postmenopausal, ER-positive (as defined by an immunohistochemistry score of >10%), and HER2-negative. Prior use of adjuvant aromatase inhibitor therapy was allowed if it had been stopped at least 1 year before study entry. Previous treatment with an aromatase inhibitor for metastatic breast cancer was not allowed. Patients were permitted to have received 0 or 1 prior chemotherapy regimens for metastatic breast cancer. Patients could have measurable or nonmeasurable disease. An Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 was required.

Patients were randomized to receive 2.5 mg of letrozole orally daily plus 100 mg of dasatinib orally daily or 2.5 mg of letrozole orally daily. Patients in the letrozole arm whose disease progressed had the option of crossing over to receive dasatinib and continue letrozole treatment.

The patients' median age was 62 years. The median disease-free intervals were similar in both arms (76 months with letrozole/dasatinib vs 77 months for letrozole). In the letrozole/dasatinib arm, 42% of patients presented with stage IV disease at their initial diagnosis, vs 32% of those in the letrozole arm. Sites of metastatic disease were balanced in the 2 arms. Approximately 50% of the patients were chemotherapy-naive. Approximately 40% of the patients in both groups had received prior tamoxifen therapy, and 10% or fewer of the patients had received prior adjuvant aromatase inhibitor therapy. In the letrozole/dasatinib group, 60% of the patients were endocrine therapy–naive, vs 49% of the patients in the letrozole group.

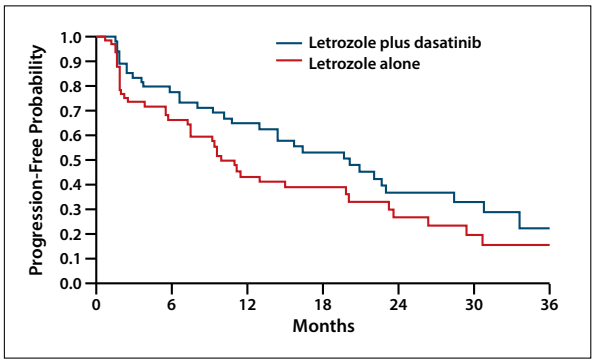

Figure 2. In a phase 2 trial comparing letrozole plus dasatinib vs letrozole alone, the median progression-free survival was 20.1 months in the combination arm and 9.9 months in the single-agent arm among patients in the intent-to-treat population. Adapted from Paul D et al. Abstract S3-07. Paper presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX.[2]

The letrozole/dasatinib combination was generally well tolerated. The grade 2 or 3 AEs that occurred were expected toxicities of dasatinib. Grade 2 or 3 rash, fatigue, edema, neutropenia, and nausea each occurred in approximately 10% of patients. Pleural effusion developed in 9% of patients. A reduction in the dasatinib dose was required in 26%.

Among the protocol-evaluable population, the clinical benefit rates did not significantly differ between the 2 arms (letrozole plus dasatinib, 71% [95% CI, 58%-83%]; letrozole, 66% [95% CI, 52%-77%]). Among the 61 patients in the letrozole arm, 35 crossed over to letrozole plus dasatinib, and these patients had a clinical benefit rate of 23%.

In the intent-to-treat population, the median PFS was 20.1 months in the letrozole/dasatinib arm and 9.9 months in the letrozole arm (Figure 2). As this phase 2 trial was a noncomparative, parallel-group study, the calculated hazard ratio (HR) of 0.69 is exploratory. In both arms, approximately one-third of patients had a baseline T-score lower than –1.5 at their worst site of osteopenia at study entry. An analysis of patients' last on-study bone mineral density results showed that T-scores below –1.5 were less common in the letrozole/dasatinib arm (14%) than in the letrozole arm (32%). In both arms, approximately one-third of patients were treated with a bisphosphonate.

In conclusion, letrozole plus dasatinib had a 71% clinical benefit rate as first-line aromatase inhibitor treatment for

metastatic breast cancer. This clinical benefit rate was not significantly different from that of letrozole alone (66%). In this noncomparative, parallel-group, phase 2 study, patients treated with letrozole plus dasatinib had a promising median PFS of 20.1 months. The patients treated with letrozole alone had a median PFS of 9.9 months. These findings suggest that dasatinib may inhibit the emergence of acquired resistance to aromatase inhibitor therapy.

Previous studies have shown that in patients treated with a nonsteroidal aromatase inhibitor, the addition of dasatinib to fulvestrant or exemestane did not improve PFS over each agent alone.[9] These findings suggest that dasatinib may be of benefit mainly in patients who receive it as initial aromatase inhibitor therapy.

Dasatinib at a daily oral dose of 100 mg was generally well tolerated and had no unexpected toxicities. Dasatinib may decrease the incidence of osteopenia in patients on aromatase inhibitor therapy. Biomarkers that are putative and predictive of benefit from dasatinib will be assessed in the archive of breast cancer tissues to help inform patient selection in future studies.

P3-13-03 A Phase III, Open-Label, Randomized Study of Eribulin Versus Capecitabine in Patients With Metastatic Breast Cancer: Effect of Post-Progression Anti-Cancer Treatments and Metastatic Progression Events on Overall Survival[10]

A Awada, PA Kaufman, L Yelle, J Cortes, J Wanders, J O'Shaughnessy, MS Olivo, Y He, F Garzon, CE Dutcus, TA Binder, C Twelves, EA Perez

This post hoc analysis of a phase 3, open-label study examined the impact of postprogression anticancer treatment in patients with locally advanced or metastatic breast cancer randomized to receive eribulin (n=554) or capecitabine (n=548).[10,11] The patients had received an anthracycline and a taxane (≤2 prior chemotherapy regimens for advanced disease). The trial showed a trend favoring eribulin over capecitabine for overall survival (OS; 15.9 months vs 14.5 months) but not PFS (4.1 months vs 4.2 months).

This study investigated the discord between OS and PFS by assessing whether OS was impacted by postprogression anticancer treatment or crossover to capecitabine. After discontinuing the study treatment, 70.4% of patients in the eribulin arm and 62.0% in the capecitabine arm received further anticancer therapy. Analysis of exploratory postprogression anticancer treatment subgroups suggested that the trend in OS favoring eribulin over capecitabine was likely not attributable to crossover to capecitabine or another subsequent treatment (Figure 3). Patients in the eribulin arm who received capecitabine at any time did not have an improved OS (HR, 1.01; 95% CI, 0.78-1.31), and no significant differences in OS were observed between different postprogression anticancer treatments for patients in the eribulin arm.

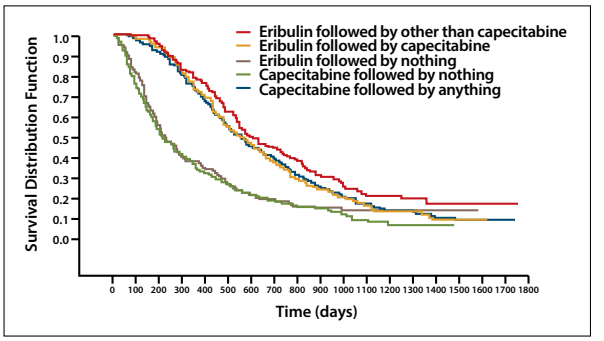

Figure 3. Analysis of exploratory postprogression anticancer treatment subgroups in a phase 3 trial of eribulin vs capecitabine suggested that a trend in overall survival favoring eribulin over capecitabine was likely not attributable to crossover to capecitabine or another subsequent treatment. Adapted from Awada A et al. Abstract P3-13-03. Poster presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX.[10]

A worse prognosis was seen when progression was caused by the development of new metastases rather than an increase in the size of a preexisting lesion. The appearance of new metastases was highly correlated with worse OS (HR, 2.1; 95% CI, 1.8-2.4; Wald $P<.0001$). The authors suggested that the discord in PFS and OS may relate to the consequences of these different progressive events.

S5-04 Primary Results of ROSE/TRIO-12, a Randomized Placebo Controlled Phase III Trial Evaluating the Addition of Ramucirumab to First-Line Docetaxel Chemotherapy in Metastatic Breast Cancer[12]

JR Mackey, M Ramos-Vazquez, O Lipatov, N McCarthy, D Kraznozhon, V Semiglazov, A Manikhas, K Gelmon, G Konecny, M Webster, R Hegg, S Verma, V Gorbounova, D Abi Gerges, F Thireau, H Fung, L Simms, M Buyse, A Ibrahim, M Martin

This randomized, placebo-controlled, phase 3 trial evaluated the addition of ramucirumab to first-line docetaxel chemotherapy in metastatic breast cancer.[12] Vascular endothelial growth factor (VEGF) receptor 2 and its ligands (VEGF-A, VEGF-C, and VEGF-D) are important mediators for angiogenesis. In human breast cancer, intensive angiogenesis is associated with a poor prognosis. Previous clinical trials of antiangiogenesis therapy in breast cancer have not demonstrated improvement in OS.

The novel agent ramucirumab is a human monoclonal antibody that targets VEGF receptor 2 and binds to the extracellular domain of this receptor, preventing the binding of the ligands VEGF-A, VEGF-C, and VEGF-D. The binding of ramucirumab shuts off endothelial cell proliferation and angiogenesis.

In 2008, the ROSE (Ramucirumab Overall Survival Evaluation)/TRIO-12 (Translation Research in Oncology) trial was designed to evaluate the addition of ramucirumab to docetaxel.[13] This trial was based on reports of synergistic interaction between ramucirumab and docetaxel, as well as the observation that the breast cancer population was appearing to benefit from antiangiogenic strategies. The trial randomized patients to 1 of 2 arms. The control arm received docetaxel intravenously at a dosage of 75 mg/m^2 every 3 weeks. The experimental arm received docetaxel intravenously at a dosage of 75 mg/m^2 every 3 weeks in combination with ramucirumab intravenously at a dosage of 10 mg/kg every 3 weeks.

Patients were treated until progressive disease, unacceptable toxicity, or withdrawal of consent. The primary endpoint was investigator-assessed PFS. Secondary endpoints were OS, time to progression, overall response rate, safety, and quality of life. The assumption was that the PFS would be 6 months in the control group and 8 months in the experimental arm, with 86% power to demonstrate this 2-month difference. At the time of the primary analysis, a survival interim analysis was performed, which was reported at the 2013 San Antonio Breast Cancer Symposium. The definitive OS analysis will be reported in the future.

Patients in this study had metastatic or unresectable locally recurrent breast cancer. They could not have received prior chemotherapy or biologic therapy for advanced disease. They had to have completed adjuvant or neoadjuvant taxanes at least 6 months before enrollment. Biologic therapy was not permitted within the previous 6 weeks before study enrollment, and radiotherapy was not permitted within the previous 3 weeks. Patients had adequate end-organ function, an ECOG performance status of 0 to 1, and no ongoing cardiovascular risk factors. The screening for the study involved 1455 women, and 1144 were randomized (2:1). These randomized patients represented the intent-to-treat population, on which all efficacy results were based. Because 10 patients did not receive study treatment, the safety population was 1134 patients.

Patient characteristics were evenly distributed between the 2 arms, with symmetric distribution of ECOG performance status, number of metastatic sites, presence of visceral disease, and prior taxane therapy. Approximately one-quarter of patients had received prior taxanes in the neoadjuvant or adjuvant setting. Three-quarters of the patients had hormone receptor–positive disease, and the remaining one-quarter had triple-negative breast cancer.

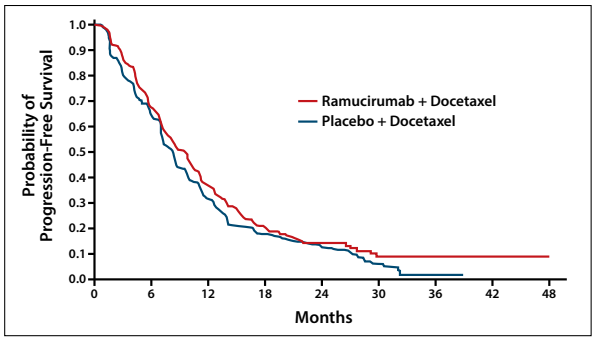

Figure 4. In a phase 3 trial evaluating the addition of ramucirumab to first-line docetaxel chemotherapy in metastatic breast cancer, the median investigator-assessed progression-free survival was 9.5 months with ramucirumab plus docetaxel and 8.2 months for docetaxel plus placebo, a difference that was not statistically significant. Adapted from Mackey JR et al. Abstract S5-04. Paper presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX.[12]

The median investigator-assessed PFS was 9.5 months with ramucirumab plus docetaxel and 8.2 months for docetaxel plus placebo (HR, 0.88; 95% CI, 0.75-1.01; *P*=.077; Figure 4). The planned sensitivity analysis, which was an independent radiologic review of the response and a determination of the PFS endpoint, found that the PFS was 11.1 months in the ramucirumab-plus-docetaxel arm and 8.6 months in the control arm (HR, 0.79; 95% CI, 0.67-0.94; *P*=.008). These values were similar to the investigator-assessed PFS values. Although the *P* value to this difference appeared to be significant, it should be mentioned that this study was a sensitivity analysis, and the *P* value should not be interpreted as a positive sign because the primary analysis was negative.

OS was not significantly increased among patients in the ramucirumab-plus-docetaxel arm (HR, 1.01; 95% CI, 0.83-1.23; *P*=.915). The median OS was 27 months at this interim analysis. Final OS data were still being collected.

Subgroup PFS analyses found that no particular group of patients derived benefit from allocation to ramucirumab rather than placebo. The overall response rate increased to 44.7% in the ramucirumab-and-docetaxel arm from 37.9% in the placebo-and-docetaxel arm. The median time to progression was 9.7 months with ramucirumab and 8.2 months with placebo (HR, 0.78). The administration of treatment for both arms was similar, with the median duration of therapy and the range of therapies identical apart from randomization.

Treatment-emergent AEs occurring in more than 10% of patients included fatigue, stomatitis, epistaxis, increased lacrimation, hypertension, decreased weight, decreased appetite, increased hand-foot syndrome, and

insomnia. Among the hematologic AEs, febrile neutropenia occurred at a higher rate in the ramucirumab arm. AEs of special interest in an antiangiogenic trial that were increased in the ramucirumab arm included bleeding, which was generally low-grade epistaxis; hypertension; proteinuria; and gastrointestinal perforation. Notably, the number of venous thrombotic events was higher in the placebo-plus-docetaxel arm than in the ramucirumab-plus-docetaxel arm.

In conclusion, the ROSE/TRIO-12 trial demonstrated that ramucirumab plus docetaxel did not significantly prolong the primary endpoint of investigator-assessed PFS when compared with placebo plus docetaxel (HR, 0.88; *P*=.077). In the sensitivity analysis, PFS was slightly longer in the ramucirumab-plus-docetaxel arm (HR, 0.79; *P*=.008). At the time of this interim analysis, no difference had been observed in OS, although overall response rate and disease control rates were higher and time to progression was longer in the patients receiving ramucirumab and docetaxel. No subgroup derived particular benefit from ramucirumab, as defined by the clinical criteria in the protocol. The combination of ramucirumab plus docetaxel was associated with higher rates of AEs, which included fatigue, hypertension, bleeding, febrile neutropenia, and stomatitis.

P3-13-05 Eribulin Mesylate as First-Line Therapy for Locally Recurrent or Metastatic HER2-Negative Breast Cancer: Results of a Phase 2, Multicenter, Single-Arm Study[14]

K McIntyre, J O'Shaughnessy, L Schwartzberg, S Glück, E Berrak, J Song, J Rege, D Cox, L Vahdat

This first-line study of eribulin examined its objective response rate as a single agent in 56 patients with locally recurrent or metastatic HER2-negative breast cancer.[14] All patients in the trial received at least 1 dose of eribulin. The median number of cycles received was 7, and 32 of the patients received at least 6 cycles. Three-quarters of the patients (n=42) had received prior anticancer therapy; 48% (n=27) had received anthracycline therapy, and 68% (n=38) had received neoadjuvant or adjuvant therapy.

The objective response rate was 28.6% (95% CI, 17.3%-42.2%), with a similar rate (27.3%) in patients who had received neoadjuvant or adjuvant treatment with anthracyclines and/or taxanes. The clinical benefit rate was 51.8% for all patients and 45.5% for those who had received prior anthracyclines and/or taxanes. The median PFS was 6.8 months for all patients, 7.4 months for patients with estrogen receptor–positive breast cancer, and 3.4 months for patients with triple-negative breast cancer. Median PFS did not differ between patients who had received prior anthracyclines and/or taxanes (5.9 months) and those who had not (5.7 months). In most patients, the sum of target lesion diameters decreased from measurement at baseline to the postbaseline nadir (Figure 5).

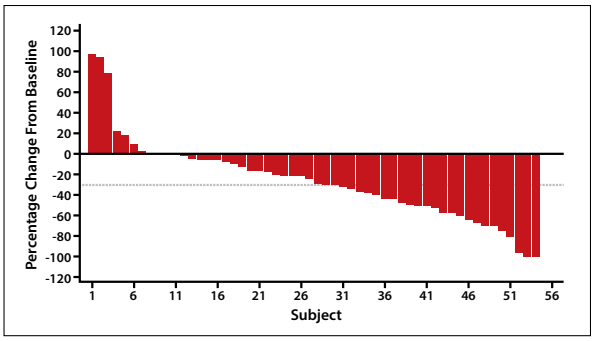

Figure 5. In a phase 2 study of eribulin mesylate as first-line therapy for locally recurrent or metastatic HER2-negative breast cancer, most patients experienced a decrease in the sum of target lesion diameters from baseline to postbaseline nadir, as measured by RECIST criteria. HER2, human epidermal growth factor receptor 2; RECIST, Response Evaluation Criteria in Solid Tumors. Adapted from McIntyre K et al. Abstract P3-13-05. Poster presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX.[14]

The most common AEs affecting at least 25% of patients were alopecia, neutropenia, fatigue, peripheral neuropathy, nausea, anemia, leukopenia, constipation, and diarrhea. Grade 3 or 4 AEs, which occurred in 36 patients, consisted of neutropenia, fatigue, peripheral neuropathy, anemia, and leukopenia. Treatment-related serious AEs occurred in 5 patients; they included febrile neutropenia in 3 patients, neutropenia in 3 patients, and leukopenia in 1 patient. This safety profile is consistent with the known profile for eribulin. AEs led 6 patients to discontinue treatment.

P2-16-23 The ENCHANT-1 Trial (NCT01677455): An Open Label Multicenter Phase 2 Proof of Concept Study Evaluating First Line Ganetespib Monotherapy in Women With Metastatic HER2 Positive or Triple Negative Breast Cancer (TNBC)[15]

A Awada, N Spector, I El-Hariry, AA Rodriguez, JK Erban, J Cortes, H Gomez, A Kong, T Hickish, L Fein, L Vahdat, I MacPherson, J-L Canon, S Mansoor, A Giovanne, K McAdam, VM Vukovic, I Yalcin, R Bradley, D Proia, MS Mano, EA Perez, DA Cameron

Ganetespib is a second-generation inhibitor of heat shock protein 90. Inhibition of this protein can block multiple oncogenic pathways implicated in the initiation and progression of different subtypes of breast cancer. Ganetespib is being

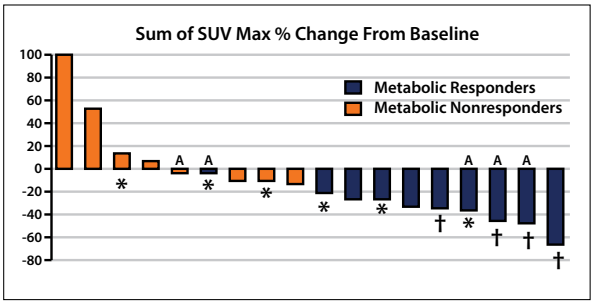

Figure 6. Metabolic response in a phase 2 proof-of-concept study evaluating first-line ganetespib in women with metastatic HER2-positive or triple-negative breast cancer. A, Cohort A (HER2-positive, n=5).*Corresponding stable disease by RECIST 1.1 (n=6). †Corresponding objective response by RECIST 1.1 (n=4). HER2, human epidermal growth factor receptor 2; RECIST, Response Evaluation Criteria in Solid Tumors; SUV, standardized uptake value. Adapted from Awada A et al. Abstract P2-16-23. Poster presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX.[15]

tested as a first-line monotherapy agent in a phase 2 study in patients with locally advanced, metastatic HER2-positive or triple-negative breast cancer. Enrollment is ongoing. At the time of this interim analysis, the study had enrolled 5 patients with HER2-positive breast cancer and 15 patients with triple-negative breast cancer, but no patients with estrogen receptor–positive or progesterone receptor–positive breast cancer. The patients will receive ganetespib as a single agent at 150 mg/m^2 twice weekly for 3 of 4 weeks.

A metabolic response, as determined by investigator review, occurred in 4 of 5 patients with HER2-positive breast cancer and in 6 of 13 patients with triple-negative breast cancer (Figure 6). Independent review of the metabolic response identified 3 of 4 patients with HER2-positive breast cancer as responders, and 4 of 11 patients with triple-negative breast cancer as responders. These early metabolic responses appeared to correlate with the objective responses. Of 4 patients with HER2-positive breast cancer evaluated by investigator review, 2 had a partial response and 2 had stable disease. Of 11 patients with triple-negative breast cancer evaluated by investigator review, 2 had a partial response, 4 had stable disease, and 5 had progressive disease. Independent review of objective responses in 4 patients with HER2-positive breast cancer identified 1 with a complete response, 2 with a partial response, and 1 with stable disease; independent review of objective responses in 11 patients with triple-negative breast cancer identified 2 with a partial response, 5 with stable disease, and 4 with progressive disease. The 1 patient with triple-negative breast cancer who had a complete response had no anomalies on physical examination at week 12 (3 cycles) and converted to operable disease that was treated by mastectomy with axillary clearance.

The main AE was diarrhea. AEs affecting 10% or more of patients (n=20) were diarrhea, fatigue, nausea, decreased appetite, increased ALT, insomnia, increased AST, constipation, peripheral edema, abdominal pain, musculoskeletal pain, and vomiting. Grade 3 AEs included diarrhea, fatigue, decreased appetite, increased ALT, increased AST, and vomiting. No grade 4 or 5 events occurred.

P4-12-12 Phase 2, Multicenter, Single-Arm Study of Eribulin Mesylate + Trastuzumab as First-Line Therapy for Locally Recurrent or Metastatic HER2-Positive Breast Cancer[16]

S Wilks, S Puhalla, J O'Shaughnessy, L Schwartzberg, E Berrak, J Song, J Rege, D Cox, L Vahdat

Eribulin mesylate was combined with trastuzumab as first-line therapy for locally recurrent or metastatic HER2-positive breast cancer in this phase 2 trial. The study enrolled 52 patients, and 45 completed the treatment phase, which consisted of 6 cycles of eribulin at 1.4 mg/m^2 on days 1 and 8 of each 21-day cycle and trastuzumab at 8 mg/kg on day 1 of cycle 1 and on day 1 of each subsequent 21-day cycle. The 9 patients who discontinued did so because of treatment-emergent AEs (n=3), progressive disease (n=3), or other reasons (n=3).

The objective response rate was 71.2% (95% CI, 56.9%-82.9%), and the median PFS was 11.6 months (95% CI, 9.1-13.9). Three patients (5.8%) achieved a complete response, and 34 patients (65.4%) achieved a partial response. Stable disease occurred in 13 patients (25.0%), and 1 patient (1.9%) experienced progressive disease. Clinical benefit, which included complete response, partial response, and stable disease for 6 or more months, was observed in 44 patients (84.6%; 95% CI, 71.9%-93.1%). Disease control, a compilation of complete responses, partial responses, and stable disease, was observed in 50 patients (96.2%; 95% CI, 86.8%-99.5%). The median change in the target lesion diameter was –62.4% from baseline. The median time to first response was 1.3 months (95% CI, 1.2-1.4).

The patients received a median of 10.0 cycles of eribulin and 11.0 of trastuzumab. All patients experienced treatment-emergent AEs, which were grade 3 or higher in 71.2%. Serious treatment-emergent AEs occurred in 15 patients (28.8%); they included neutropenia in 8 (15.4%), febrile neutropenia in 4 (7.7%), peripheral neuropathy in 3 (5.8%), and vomiting in 3 (5.8%). One patient died from chronic heart failure 15 days after the last dose of the study treatment; this death may have been related to the study drug.

The most common treatment-emergent AEs of all grades that affected at least 25% of patients were alopecia,

fatigue, peripheral neuropathy, neutropenia, nausea, diarrhea, anemia, constipation, and decreased appetite. The most common grade 3/4 treatment-emergent AEs were neutropenia, which occurred in 20 patients (38.5%), and peripheral neuropathy, which occurred in 14 patients (26.9%). Other grade 3/4 treatment-emergent AEs included fatigue, nausea, diarrhea, and anemia.

S5-07 SWOG S0500—A Randomized Phase III Trial to Test the Strategy of Changing Therapy Versus Maintaining Therapy for Metastatic Breast Cancer Patients Who Have Elevated Circulating Tumor Cell (CTC) Levels at First Follow-Up Assessment[17]

JB Smerage, WE Barlow, DF Hayes, EP Winer, B Leyland-Jones, G Srkalovic, S Tejwani, AF Schott, MA O'Rourke, DL Lew, JR Gralow, RB Livingston, GN Hortobagyi

The Southwest Oncology Group (SWOG) S0500 study is a randomized phase 3 trial to test the strategies of changing therapy vs maintaining therapy in patients with metastatic breast cancer who have elevated circulating tumor cells (CTCs) at first follow-up assessment.[17] CTCs are cancer cells detected in peripheral blood. They have been detected in a wide variety of malignancies, including cancers of the breast, prostate, lung, colon, and ovary.

SWOG S0500 used a system cleared by the FDA to assess prognosis and monitor therapy in patients with metastatic breast cancer. The platform uses a 2-step detection process. First, CTCs are immunopurified from 7.5 mL of whole blood on the basis of their expression of the epithelial cell adhesion marker. Then, immunofluorescence microscopy is used to confirm and count the CTCs based on dual staining with the nuclear stain diamidino-2-phenylindole and a pan-cytokeratin antibody. White blood cells are excluded by CD45 staining.

CTC levels are highly prognostic when measured before the initiation of first-line chemotherapy or subsequent lines of therapy and at first follow-up after the start of a new chemotherapy regimen.[18-20] In an earlier study by Cristofanilli and associates, patients with elevated CTCs after 1 cycle of chemotherapy had a very short PFS of 2.1 months.[18] This finding, which was interpreted to mean that these patients were likely receiving ineffective therapy, served as the primary basis for the SWOG S0500 study. The hypothesis was that patients with metastatic breast cancer who continued to have elevated CTCs after 1 cycle of first-line chemotherapy would benefit from a change to an alternative chemotherapy regimen. The underlying assumption was that patients would have better outcomes if they experienced less cumulative toxicity from ineffective therapy, and that switching would increase the chance that their therapy would be effective. The primary endpoint was OS. Secondary endpoints included PFS and the correlation of CTC levels to OS and PFS at baseline and first follow-up.

A CTC test was performed at baseline, before patients began cycle 1 of first-line cytotoxic chemotherapy. An elevated CTC level was defined as 5 or more CTCs per 7.5 mL of whole blood. Patients with fewer than 5 CTCs at baseline were assigned to arm A, an observation arm. Patients with more than 5 CTCs underwent a second CTC test on day 21. Those patients with levels that decreased to less than 5 were assigned to arm B, another observation arm. Patients whose levels remained at 5 or higher were randomized to continue current therapy until clinical evidence of progression or to immediately switch to a new chemotherapy for cycle 2. Remaining on current therapy was considered the standard of care.

The key eligibility criteria included histologically confirmed breast cancer with at least clinical evidence of metastatic disease. Disease could be measurable or, if not measurable, it had to include bone disease. Patients could not have received prior chemotherapy for metastatic disease; however, prior therapy with an endocrine agent, a bisphosphonate, or another biologic agent, such as trastuzumab, was allowed. Prior adjuvant chemotherapy must have been completed 12 months before registration. The HER2 status of the tumor had to be known because it was a stratification factor, along with measurable disease vs bone-only disease.

The trial was designed to mimic standard-of-care therapy. The choice of cytotoxic chemotherapy was made by the treating physician, both at the beginning of the trial and after a switch. Biologic therapies, such as trastuzumab and bevacizumab, were allowed. Biologic agents that started with cycle 1 were continued for subsequent cycles, regardless of whether the chemotherapy regimen was maintained or switched. Patients were permitted to stop therapy because of intolerable toxicity; in such cases, an alternative therapy could be initiated, regardless of the treatment arm. If a patient had no evidence of progression for at least 24 weeks, cytotoxic chemotherapy could be stopped at the discretion of the treating physician to provide a chemotherapy holiday. In this situation, endocrine therapy could be initiated. Cytotoxic chemotherapy, if stopped, could not resume until disease progression.

The trial registered a total of 624 patients, although 29 were excluded from analysis because they were found to be ineligible or because a baseline CTC result was not obtained. Among the baseline population, 319 patients (54%) had elevated CTCs at baseline. CTC results at day 21 were not available for 33 patients, for reasons such as death, progres-

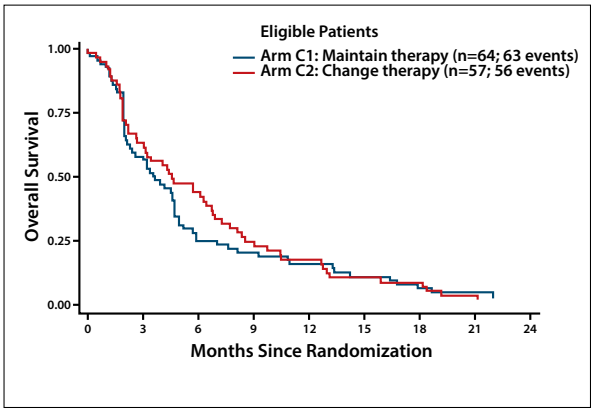

Figure 7. In a phase 3 trial testing the strategies of maintaining therapy (Arm C1) vs changing therapy (Arm C2) in metastatic breast cancer patients with elevated circulating tumor cells, progresssion-free survival did not differ between the arms. HR, hazard ratio. Adapted from Smerage JB et al. Abstract S5-07. Paper presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX.[17]

sion, and patient refusal. After 1 cycle of chemotherapy, the CTC counts of 163 patients (57%) dropped to below 5 CTCs per 7.5 mL of whole blood. Therefore, a total of 123 patients (43%) were treated in the randomized arms and either continued treatment with their current therapy or switched at cycle 2 to a new therapy.

There was no difference in OS between the 2 randomized arms. The median OS was 12 months for both groups, and the Kaplan-Meier curves overlapped (HR, 1.01; *P*=.83). Subset analyses demonstrated no significant differences based on age, triple-negative phenotype, HER2 status, or hormone-receptor status. In all of these groups, the confidence intervals crossed unity on the forest plots, where the HR is 1.0. Similarly, no significant difference in PFS was observed between the 2 randomized arms. The median PFS was 3.5 months in the continued-therapy group and 4.6 months in the switch group (HR, 0.91; *P*=.61; Figure 7).

The dramatic difference in patients' prognoses according to CTC status was confirmed by this study and is its most notable result. The patients with low CTC counts at baseline had a substantially better median OS (35 months), with more than 25% living longer than 5 years. The patients with elevated CTC counts, both at baseline and at day 21, had a remarkably poor prognosis for first-line chemotherapy. Their median OS was 13 months, and 75% died at just over 18 months. In patients whose CTC counts converted from high to low, the intermediate median OS was 23 months. PFS had a similar separation of curves; patients with elevated CTC counts at both time points had a median PFS of 4.9 months.

The authors noted that the study was not designed to investigate the effects of chemotherapy, and it would be incorrect to interpret the outcome as evidence that chemotherapy had no benefit. Those patients who continued to have elevated CTC counts after 1 cycle of first-line chemotherapy had a relatively short OS. The elevated level of risk associated with their disease might justify early consideration of these patients for clinical trials of novel agents. Patients with low CTC counts at baseline have a much better prognosis than those whose CTC counts remained elevated after 1 cycle of first-line therapy, with median OS times of 35 months and 13 months, respectively. Patients whose CTC counts converted to a low number after 1 cycle had an intermediate prognosis.

At the time the study was designed, the existing technology allowed primarily only the counting, or enumeration, of CTCs. Current technology permits molecular analyses of CTCs. Protein expression, ribonucleic acid expression, and mutational analyses are all being investigated by many groups. It is hoped that these molecular analyses will be able to not only predict prognosis but also to identify the most effective therapeutic strategies.

P3-13-04 Effect of Age on Tolerability and Efficacy of Eribulin and Capecitabine in Patients With Metastatic Breast Cancer Treated in Study 301[21]

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

This post hoc exploratory analysis examined the effects of age in 1102 patients with locally advanced, metastatic breast cancer who had participated in an open-label, randomized, multicenter, phase 3 trial.[11] The trial found a nonstatistically significant trend favoring eribulin over capecitabine for OS but not PFS. The trial randomized 554 patients to eribulin. Most patients (n=468 [85%]) were ages 65 years or younger. Among the 548 patients randomized to capecitabine, 10.4% (n=57) were older than 65 years and 89.6% (n=491) were 65 or younger.

The proportion of AEs was numerically higher among the older patients in both treatment arms.[21] Among patients in the eribulin arm, 70.2% of the older patients and 64.6% of the younger patients experienced grade 3 or 4 AEs. Among patients in the capecitabine arm, 54.4% of the older patients and 45.0% of the younger patients experienced grade 3 or 4 AEs.

There was no significant increase in study withdrawal owing to AEs in the older patients who received eribulin (10.7% of those >65 years withdrew vs 7.4% of those ≤65 years). Among patients in the capecitabine arm, however, elderly patients withdrew at more than twice the rate of younger patients (21.1% of those >65 years withdrew vs 9.2% of those ≤65 years). Both age groups had similar exposures to the study drugs.

With eribulin treatment, OS was not statistically different between the age groups (*P*=.27). Eribulin treatment trended toward improved median OS compared with capecitabine treatment (age >65 years, 18.4 vs 14.1 months; HR, 0.74; 95% CI, 0.50-1.12; and age ≤65 years, 15.8 vs 14.5 months; HR, 0.90; 95% CI, 0.78-1.04).

P2-16-01 A Randomized, Phase II, Multicenter, Double-Blind, Placebo-Controlled Trial Evaluating Onartuzumab With or Without Bevacizumab in Combination With Weekly Paclitaxel in Locally Recurrent or Metastatic Triple-Negative Breast Cancer (TNBC)[22]

V Dieras, D Yardley, G Romieu, V Valero, S Isakoff, H Koeppen, H Thurm, M Teng, M Campone, S Mocci

Dysregulation of the hepatocyte growth factor (HGF)/MET pathway is present in many malignancies, and overexpression of MET is associated with a poor prognosis in patients with triple-negative breast cancer. The recombinant, humanized, monovalent, monoclonal antibody onartuzumab is directed against MET. Onartuzumab selectively blocks ligand binding, thus preventing HGF activation.

This phase 2, multicenter, double-blind, placebo-controlled trial enrolled 185 patients who had locally recurrent or metastatic triple-negative breast cancer and had received 1 or no prior therapies for metastatic disease. The patients were randomized (1:1:1) to receive paclitaxel, bevacizumab, and onartuzumab; paclitaxel and onartuzumab; or paclitaxel and bevacizumab (control arm). The patients were stratified by the number of metastatic sites (<3 vs ≥3), number of prior metastatic breast cancer regimens (1 vs 2), and disease-free interval if they were first-line patients (≤6 vs >6 months).

The median PFS was 7.3 months with paclitaxel, bevacizumab, and onartuzumab (HR vs control, 1.08; 95% CI, 0.69-1.70); 5.4 months with paclitaxel and onartuzumab (HR vs control, 1.74; 95% CI, 1.13-2.78); and 7.2 months with paclitaxel and bevacizumab. The median OS was 14.7 months with paclitaxel, bevacizumab, and onartuzumab (HR vs control, 1.35; 95% CI, 0.74-2.44); 13.4 months with paclitaxel and onartuzumab (HR vs control, 1.88; 95% CI, 1.00-3.54); and 17.4 months with paclitaxel and bevacizumab. The most frequent AEs were peripheral edema, fatigue, and diarrhea, with no new safety signals observed. Overall, adding onartuzumab to either the combination of paclitaxel and bevacizumab or paclitaxel alone did not improve PFS or other clinical outcomes compared with the control treatment of paclitaxel and bevacizumab.

P3-03-07 Combination of Eribulin and PI3K Inhibitors in Triple Negative and HER2 Expressing Breast Cancer Cell Lines Results in Synergistic Growth Inhibition and Enhanced Inhibition of the PI3K Pathway[23]

D Luyimbazi, T Luu, Q Xing, J Yan, D Tully, E Han, RML Yip, JH Yim

Rates of expression of Akt and activation of the *PI3K* pathway are high in patients with triple-negative breast cancer. Activation of the PI3K/Akt/mammalian target of rapamycin (mTOR) pathway is a key adaptive change that drives endocrine resistance. Higher levels of Akt and consequent activation of mTOR downstream occur in triple-negative breast cancer. This study examined whether activity of the PI3K pathway and cell growth could be modulated by eribulin alone or in combination with the pan-class PI3K/mTOR inhibitors BEZ235 and BKM120.

Treatment of the triple-negative breast cancer cell line MDA468 with eribulin resulted in decreased phosphorylated Akt (pAkt) expression that began at a concentration of 10 nM. Treatment with either BEZ235 or BKM120 alone increased pAkt expression in a dose-dependent fashion, but combining either of these agents with eribulin resulted in a dose-dependent decrease in pAkt expression (Figure 8). Significant synergistic inhibition of growth occurred when eribulin and PI3K inhibitors were combined.

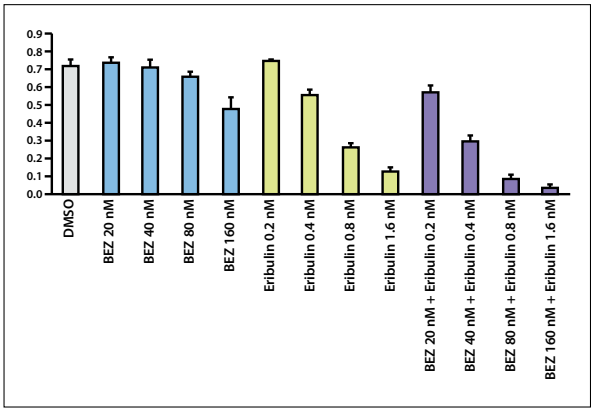

Figure 8. A dose-dependent decrease in expression of phosphorylated Akt was seen in a study of eribulin and pan-class phosphoinositide 3-kinase/mTOR inhibitors in the triple-negative breast cancer cell line MDA468. Data for the agent BEZ235 are shown. mTOR, mammalian target of rapamycin. Adapted from Luyimbazi D et al. Abstract P3-03-07. Poster presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX.[23]

P3-03-08 A Comparison of PI3K Inhibition by Eribulin, Other Microtubule Targeting Agents and a DNA-Damaging Chemotherapeutic in Triple Negative and HER2 Expressing Breast Cancer Cell Lines[24]

D Luyimbazi, T Luu, Q Xing, J Yan, D Tully, E Han, RML Yip, JH Yim

This study compared eribulin with 2 agents: vinblastine, which targets microtubules by blocking the polymerization of tubulin into microtubules, and paclitaxel, which targets microtubules by enhancing the polymerization of tubulin to microtubules and stabilizing microtubules against depolymerization. Triple-negative breast cancer is associated with higher levels of Akt and consequent activation of mTOR downstream. To determine activation of the PI3K/Akt/mTOR pathway, this study analyzed pAkt and phosphorylated Akt S6K1 (pS6K1). S6K1, which is activated by mTOR, stimulates ribosomes and initiates protein translation.

Treatment with either eribulin or vinblastine inhibited the expression of both pAkt and pS6K1 in the triple-negative breast cancer cell line MDA468, whereas paclitaxel increased pAkt expression in a dose-dependent manner. Similarly, the conventional DNA-damaging chemotherapeutic agent cisplatin also increased pAkt expression. Eribulin had a lower half-maximal inhibitor concentration (IC_{50}) for both pAkt and pS6K1 than did vinblastine. Blockading the polymerization of microtubules has a potential role in inhibiting the PI3K pathway and, thus, in treating refractory breast cancer.

PD4-1 Comparison of Mutations and Protein Expression in Potentially Actionable Targets in 5500 Triple Negative vs. Non-Triple Negative Breast Cancers[25]

JA O'Shaughnessy, Z Gatalica, JM Kimbrough, SZ Millis

This molecular profiling study evaluated gene mutations in 5521 patient samples by Sanger or Illumina sequencing, protein expression by immunohistochemistry, and gene amplification by chromogenic in situ hybridization or fluorescence in situ hybridization. The samples came from patients with metastatic breast cancers and were grouped by ER status, progesterone receptor status, and HER2 status as determined by immunohistochemistry. Of the samples, 35.8% were triple-negative breast cancers and 52.8% were either ER-positive or progesterone receptor–positive and HER2-negative; 10.9% of the patients in the cohort had cancers that were HER2-positive, with 2.4% of those positive for ER, progesterone receptor, and HER2.

The androgen receptor was expressed in 50% of cancers that were ER-negative and HER2-positive and in 18% of the cohort with triple-negative breast cancers. Nearly all androgen receptor–positive samples showed a mutation of the phosphatidylinositol-4,5-bisphosphonate 3-kinase, catalytic subunit α (*PIK3CA*) or a loss/mutation of phosphatase and tensin (PTEN), which indicates that the PI3K pathway might be activated. Therefore, inhibition of the androgen receptor and PI3K in combination should be evaluated.

Expression of the androgen receptor was associated with decreased proliferation in triple-negative breast cancer, but not in ER-positive or HER2-positive disease. Nearly all of these poor-prognosis, ER-positive cancers showed evidence that the PI3K pathway was activated, and approximately 30% had mutations of *p53*.

With the exception of mutations of *p53* and *PIK3CA*, there was a low frequency of targetable and activating mutations. Approximately 5% of breast cancers, across subtypes, may have mutations of adenomatous polyposis coli, and patients with these cancers may benefit from anti-frizzled receptor therapy. Epidermal growth factor receptor (*EGFR*) gene amplification was observed in approximately 10% of poor-prognosis, ER-positive breast cancers and 20% of ER-negative breast cancers, a finding that might help predict benefit from anti-EGFR therapy. Molecular profiling across multiple platforms is needed to identify genomic and proteomic alterations that are targetable in breast cancers with a poor prognosis.

P4-15-12 Rebastinib in Combination With Eribulin Ablates TIE2-Expressing Macrophages, Reduces Metastasis, and Increases Survival in the PyMT Metastatic Breast Cancer Model[26]

BD Smith, CB Leary, MD Kaufman, MM Hood, W-P Lu, BA Turner, S Vogeti, SC Wise, MS Berger, DL Flynn

When the vasculature of the hypoxic tumor environment is damaged by chemotherapy, radiation, or antiangiogenic treatments, rebound vascularization occurs. This process involves an angiogenic switch from the VEGF pathway to the angiopoietin/*TIE2* pathway. *TIE2*-expressing monocytes are recruited from the bone marrow, and by promoting vascularization, they lead to the growth of residual tumor cells and the progression of disease. Of note, specialized vascular structures known as *tumor microenvironment for metastases* are the location of a subset of macrophages that express *TIE2*. Macrophages in structures within the tumor microenvironment for metastases that express *TIE2* are linked to intravasation and subsequent metastasis. Rebastinib inhibits the *TIE2* kinase at picomolar concentrations and has an off-rate of more than 24 hours from *TIEs*.

This study used a syngeneic mouse breast cancer model. Polyoma middle-T antigen breast cancer cells were implanted into mammary fat pads. The primary tumor growth led to metastasis, which is modulated by TIE2-expressing monocytes and vascular structures within the tumor microenvironment for metastases.

Combining rebastinib with eribulin significantly ablated *TIE2*-expressing monocytes in the primary tumor stroma and decreased lung metastases significantly. Relative lung metastases were 100% with vehicle control. This rate was 71% with eribulin administered at 1 mg/kg 3 times per week, 71% with eribulin at 0.3 mg/kg 3 times per week, and 72% with eribulin at 0.1 mg/kg 3 times per week. Rates of relative lung metastases were further decreased with the addition of rebastinib at 10 mg/kg 2 times per week to eribulin at all dose levels (23% for 1 mg/kg, 51% for 0.3 mg/kg, and 43% for 0.1 mg/kg). The combination reduced primary tumor growth and regrowth of the tumor after resection.

PD3-3 Next Generation Sequencing Shows Clonal Selection After Treatment With Anastrozole or Fulvestrant in a Randomized Trial of Postmenopausal Patients With Large Operable or Locally-Advanced Hormone-Receptor-Positive Breast Cancer[27]

RD Iggo, HM Wood, P Rabbitts, N Quenel-Tueux, L Mauriac, G MacGrogan, H Bonnefoi

This study by Dr Richard Iggo and colleagues compared DNA copy number profiles before and after neoadjuvant treatment with anastrozole or fulvestrant in 20 patients with estrogen receptor–positive breast cancer in the HORGEN (Anastrozole or Fulvestrant in Treating Postmenopausal Patients With Breast Cancer) trial.[27,28] Samples were obtained from biopsies taken before the start of treatment and from surgically resected residual tumors after 6 months of treatment. Genomic DNA was sequenced at low depth; then, the outcomes were aligned and converted to copy number profiles. The segmented copy number profiles were clustered and then aligned on a linear scale.

After treatment, significant differences of at least 5-fold the standard deviation of the expected differences were observed in 7 tumors (35%; Table 1). Amplicon/saw-tooth profiles occurred in 3 cases. The amplicons contained *ESR1*, *FOXA1*, and *NCOA3*, which are genes involved in estrogen signaling. Profiling of sample H09 indicated that the amplicon for *ESR1* was present in some tumor cells before treatment and that new amplicons were present after treatment. The remaining 4 cases mainly had gains and losses of whole chromosomes in "simplex" profiles, in which copy number profiles became substantially simpler after treatment. Sample H13 lost chromosomes 4, 6, 11, 12, 17, and 18, and its gain of chromosome 7 disappeared.

After hormonal therapy for breast cancer, changes in the DNA copy number were common. Clonal selection, rather than de novo mutation, is the simplest explanation. The profiles that became simpler may have done so because clones with large-scale changes in copy number require survival signals provided by the estrogen receptor.

Table 1. Tumors Showing Differences in DNA Copy Number Profiles Before and After Treatment With Anastrozole or Fulvestrant

Sample	Observed Difference	Observed/ Expected	Observed/ Expected Standard Deviation
H08-Bx1–Ch1	1.79	1.26	9.10
H09–Bx1–Ch1	1.64	1.10	7.96
H010–Bx1–Ch1	1.86	1.32	9.57
H13–Bx1–Ch1	1.81	1.27	9.18
H14–Bx1–Ch1	2.29	1.75	12.67
H15–Bx1–Ch1	4.03	3.50	25.31
H19–Bx1–Ch1	1.30	0.77	5.55

Data from Iggo RD et al. Abstract PD3-3. Poster presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX.[27]

P5-08-06 PI3K Blockade Enhances the Antitumor Activity of Eribulin in *PIK3CA*-Mutant Eribulin-Resistant Tumor Xenografts[29]

V Serra, A Gris-Oliver, C Saura, M Oliveira, A Piris, YH Ibrahim, L Prudkin, JM Pérez-García, J Baselga, J Cortés

Resistance to microtubule-targeting agents may be conferred by constitutive PI3K/Akt/mTOR survival pathway activation. This study explored the concept that the antitumor activity of eribulin, a microtubule-targeting agent, may be limited by activation of the PI3K pathway, and that inhibiting PI3K may enhance this agent's efficacy.

In xenograft models, eribulin treatment occurred concomitantly with blockage of the PI3K pathway through class I pan-PI3K (BKM120) or PI3K-α-specific (BYL719) inhibition. The antitumor activity of eribulin was more limited in xenograft models of *PIK3CA* mutants compared with wild-type models of *PIK3CA*. Tumor regression occurred in *PIK3CA*-mutant xenografts that were treated concomitantly with both eribulin and a PI3K inhibitor. Wild-type models of *PIK3CA* also had increased antitumor activity with the combined therapy.

The combined therapeutic response enhanced G2/M arrest and induced apoptosis. Investigations are exploring the precise mechanism of the combination of eribulin and PI3K-targeting agents in tumor regression. These data suggest that combining PI3K inhibitors and eribulin may be of clinical benefit in patients whose breast cancer is *PIK3CA*-mutant or *PIK3CA*-wild type.

P4-12-27 Efficacy and Safety of Trastuzumab Emtansine (T-DM1) vs Lapatinib Plus Capecitabine (XL) in Patients With Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Metastatic Breast Cancer (MBC) and Central Nervous System (CNS) Metastases: Results From a Retrospective Exploratory Analysis of EMILIA[30]

I Krop, N Lin, K Blackwell, E Guardino, J Huober, M Lu, D Miles, M Samant, M Welslau, V Diéras

This retrospective exploratory analysis examined data from EMILIA (An Open-Label Study of Trastuzumab Emtansine [T-DM1] vs Capecitabine + Lapatinib in Patients With HER2-Positive Locally Advanced or Metastatic Breast Cancer), a pivotal phase 3 trial in which the antibody-drug conjugate trastuzumab emtansine prolonged PFS and OS compared with capecitabine in 991 patients with previously treated HER2-positive locally advanced or metastatic breast cancer.[31] This analysis examined data for patients who had central nervous system (CNS) metastases at baseline (n=45 in the trastuzumab emtansine arm and n=50 in the capecitabine arm) or who developed CNS metastases during the study (n=11 and n=19).

The subset of patients with CNS metastases at baseline was similar to that in the intent-to-treat population. The trastuzumab emtansine arm had significantly improved OS compared with the capecitabine arm (HR, 0.382; 95% CI, 0.184-0.795; *P*=.0081; Figure 9). This finding suggests a survival advantage with trastuzumab emtansine vs capecitabine. The patients with CNS metastases at baseline had safety profiles that were generally similar to those in the EMILIA primary analysis.

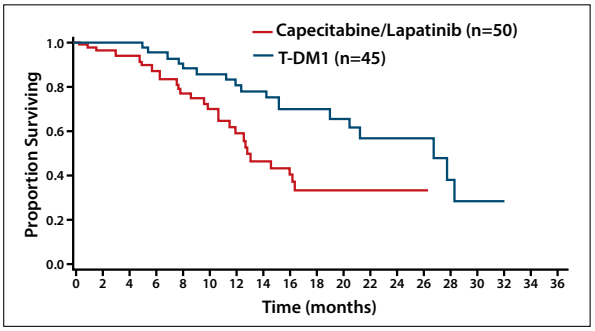

Figure 9. An analysis of data from the EMILIA trial showed that T-DM1 prolonged overall survival compared with capecitabine in patients with previously treated HER2-positive locally advanced or metastatic breast cancer and central nervous system metastases. EMILIA, An Open-Label Study of Trastuzumab Emtansine (T-DM1) vs Capecitabine + Lapatinib in Patients With HER2-Positive Locally Advanced or Metastatic Breast Cancer; T-DM1, trastuzumab emtansine. Adapted from Krop I et al. Abstract P4-12-27. Poster presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX.[30]

This study was limited because its evaluation of CNS metastases was retrospective, exploratory, and not prespecified in the statistical plan. Except at screening, the study did not have mandatory or prespecified imaging of the brain. The shorter PFS of patients in the capecitabine arm might have lowered the possibility of observing CNS progression during the study. The enrollment excluded patients with progressive CNS metastases, so the study was unable to test whether trastuzumab emtansine could shrink CNS tumors or stabilize untreated or active CNS disease. The authors concluded that the activity of HER2-directed therapies should be further investigated in a prospective study of patients with CNS metastases of metastatic breast cancer.

S4-03 Exome Sequencing Reveals Clinically Actionable Mutations in the Pathogenesis and Metastasis of Triple Negative Breast Cancer[32]

KL Blackwell, EP Hamilton, PK Marcom, J Peppercorn, N Spector, G Kimmick, J Hopkins, J Favaro, G Rocha, M Parks, C Love, P Scotland, SS Dave

Triple-negative breast cancer remains without highly effective therapeutic targets. The human genome sequencing projects tend to focus on primary tumors, not on metastatic samples. Metastatic samples are underrepresented in the literature. Recent publications have described mutations that arise only in metastatic breast cancer samples.[33,34] These findings suggest that DNA mutations in various types of breast cancer, including triple-negative or heavily pretreated metastatic tumors, might identify therapeutic targets.

Little is known regarding mutations and their correlation with clinical outcomes. This type of work has been hindered by the difficulties encountered in identifying tumor samples from patients who have received similar, if not identical, treatment. Sequential or metastatic biopsies are often not obtained in therapeutic trials because of several limiting factors, including cost, patient preference, and the balance between biopsy risk and the potential for actionable results.

The ABC (Nab-paclitaxel/Bevacizumab/Carboplatin Chemotherapy in First-Line Triple Negative Metastatic Breast Cancer) study was a phase 2, multicenter trial in which patients with first-line, metastatic triple-negative breast cancer received nab-paclitaxel at a dose of 100 mg/m^2 and carboplatin at a dose of an area under the curve of 2 on days 1, 8, and 15.[35] Patients also received bevacizumab at a dosage of 10 mg/kg on days 1 and 15 of a 28-day cycle. The primary endpoint of this study was tolerability, and the regimen was well tolerated. The most common grade 3 AEs were neutropenia and thrombocytopenia.

Samples from each patient underwent genomic analyses with metastatic biopsy, germline DNA, and primary tumor block. A biopsy of metastatic disease was required of all patients before the trial therapy was initiated. Germline DNA was collected via a buccal swab. Primary tumor samples, which came from the in-breast tumor, were collected from paraffin blocks.

The patients in the total trial population and those in the genomic analysis had similar characteristics. The median age was 50 years. The median PFS of the total trial population was 9.2 months,[35] and the current genomic analysis found a median PFS of 14.6 months. The median OS was similar for both groups (21.6 months as previously reported vs 21.9 months for the genomic analysis population).

Between July 2007 and October 2011, 44 patients consented to the trial, although metastatic tissue was not obtained from 6 because screening failed or the patient enrolled in the study for second-line therapy. Of the remaining 38 patients, 34 went on to receive therapy per the study protocol, and therefore 102 unique and adequate DNA samples were attained for exome sequencing. For this analysis, the majority of the samples were matched triplets of germline, primary, and metastatic DNA or doublets of normal and primary DNA. Of the 31 metastatic biopsies, most were obtained either from the liver or from nonbreast chest wall metastatic disease.

For the mutational analysis, DNA was extracted with standard column-based methods. The analysis had more than 5 billion sequencing reads, with a mean exome coverage of 50-fold to 100-fold. The variants were further classified as 81,383 missense variants, 1700 nonsense or stop-gain variants, and 2282 frameshift mutations corresponding to 18,638 unique genes. These variants were further narrowed to 362 nonsynonymous variants and 122 unique genes by retaining only somatic rare variants and discarding variants that affected only 1 gene in a single patient.

The Wald test identified relationships between genes with mutations and measures of clinical outcomes. Given the small sample size, the Wald test for clinical outcome analysis was not adjusted for multiple comparisons.

When the frequency distribution for the most commonly mutated somatic genes that occurred in the entire data set was examined, a mean of 10 mutations per sample was observed. Multiple patients had tumors with 122 mutated genes. Mutations occurred in 3 or more patients in 74 genes. A cosmetic data search identified genes that were confirmed or potential cancer targets.

When all of the germline DNA was screened for susceptibility mutations, only 1 mutation of *BRCA2* was identified in a known carrier. The most frequently occurring mutations from the entire tissue set were determined, independently of whether they were found in the primary sample or only in the metastatic sample. Nearly one-third of all the samples had mutated *p53*. The other most commonly mutated genes included *TACC2*; *DYNC1H1*, a heavy-chain component of the dynein family; *LAMA3*; and genes that encode the adenosine triphosphate–binding cassette transporters and transmembrane proteins. Mutations to the genes for *PI3K* and mTOR were observed in 4 patients (12%). The mutations were predominantly missense, single-nucleotide-type variants, with approximately 8% of the mutations being stop-gain or frameshift mutations.

Functional grouping of all the mutations in the data set according to gene ontology found that the enriched gene categories were related to DNA repair, phosphorus metabolism, response to DNA damage, biopolymer metabolism, response to endogenous stimulus, and cell adhesion. The most frequently mutated genes in this study's data set of 34 triple-negative breast cancer tumors were compared with those from 2 other triple-negative breast cancer genomic sequencing data sets.[36,37] Only 2 genes with mutations, those for *p53* and *PI3K*, occurred at the same frequency in all 3 data sets.

The secondary objective of this study was to compare mutations that occurred in both the primary and the matched tumor vs mutations that were seen in only the metastatic tumor sample and not in the primary sample. A total of 362 unique mutations were identified in the data set; 331 (91.4%) occurred in both the primary tumor and the matched metastatic sample, whereas 31 (8.6%) occurred in only the metastatic sample and not in the matched primary sample. Among the mutations found in only the metastatic sample and not in the matched primary sample, 84% were missense and the remaining 16% were either stop-gain or frameshift mutations. Of the 31 genes with mutations located in only the metastatic sample and not in the matched primary sample, 3—*DYNC1H1*, *TRPM2*, and *TMEM62A*—were mutated in more than 1 patient.

The final objective of the study was to correlate mutated genes with clinical outcomes. Poor PFS or poor response to therapy was correlated with *WNK1*, *TP35*, *JAK1*, and *DCHS2*. A more favorable PFS or response to therapy was correlated with *ATXN7* and *MST1*.

Although the sample sizes were very small, a significant, single-gene ontology grouping of 4 of the 6 gene mutations correlating with PFS emerged. The functional grouping of the genes involved—*WNK1*, *TP53*, *JAK1*, and *MST1*—relates to macromolecule or microtubule metabolism. These associations will require further study, but the association of this functional grouping related to microtubule maintenance is interesting to note in the setting of therapy with a taxane and an antiangiogenic agent.

Disease-free interval was associated with mutations in 8 genes: *HGF*, *PLXNA3*, *CSDE1*, *ZNF710*, *CNN2*, *PAPLN*, *SETBP1*, and *MTOR*. Disease-free interval was defined as time from the initial diagnosis or de novo

diagnosis of nonmetastatic breast cancer to the first day of treatment in the clinical trial. Interestingly, all genes with mutations correlated with a favorable prognosis or a longer disease-free interval.

Finally, 4 genes with mutations were associated with OS. Worse OS was conferred by mutations in 3 genes: *TP53*, *ITSN2*, and *ALDH8A1*. Improved OS was conferred by *SPHKAP*. The only gene that conferred worse PFS and OS when it was mutated was the gene for *p53*. No functional ontology groups were significant for the 4 mutations associated with OS.

Overall, this analysis correlated gene mutations with clinical outcomes in patients receiving first-line therapy for triple-negative breast cancer with a taxane, carboplatin, and bevacizumab. The potential actionable mutations currently being studied in breast cancer are those of *p53*, PARP, ER, JAK1, and MTOR. Actionable mutations that have the potential for study in triple-negative breast cancer include those of dynein, *MST1*, *ROS1*, *HGF*, and *ALD8A1* (also known as *aldehyde dehydrogenase 8A*).

In conclusion, this study found that the majority (91.4%) of somatic mutations are found in both the primary tumor and the matched metastatic sample. This study also found specific gene mutations that correlated with clinical outcome and suggested therapeutic targets. Further study of this tissue set for chromosomal rearrangement/loss, mutation activation status, and transcriptional analysis is under way.

References

1. Giordano SB, Jeruss JS, Bethke KP, et al. Neoadjuvant phase II trial with carboplatin and eribulin in triple negative breast cancer patients. Poster presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX. Abstract P3-14-14.
2. Paul D, Vukelja SJ, Holmes FA, et al. Letrozole plus dasatinib improves progression-free survival (PFS) in hormone receptor-positive, HER2-negative postmenopausal metastatic breast cancer (MBC) patients receiving first-line aromatase inhibitor (AI) therapy. Paper presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX. Abstract S3-07.
3. Zhang XH, Wang Q, Gerald W, et al. Latent bone metastasis in breast cancer tied to Src-dependent survival signals. *Cancer Cell.* 2009;16(1):67-78.
4. Vallabhaneni S, Nair BC, Cortez V, et al. Significance of ER-Src axis in hormonal therapy resistance. *Breast Cancer Res Treat.* 2011;130(2):377-385.
5. Renoir JM, Marsaud V, Lazennec G. Estrogen receptor signaling as a target for novel breast cancer therapeutics. *Biochem Pharmacol.* 2013;85(4):449-465.
6. Chen Y, Guggisberg N, Jorda M, et al. Combined Src and aromatase inhibition impairs human breast cancer growth in vivo and bypass pathways are activated in AZD0530-resistant tumors. *Clin Cancer Res.* 2009;15(10):3396-3405.
7. Kantarjian H, Shah NP, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med.* 2010;362(24):2260-2270.
8. Garcia-Gomez A, Ocio EM, Crusoe E, et al. Dasatinib as a bone-modifying agent: anabolic and anti-resorptive effects. *PLoS One.* 2012;7(4):e34914.
9. Strauss L, O'Shaughnessy J, Jackson J, et al. Three parallel randomized phase II trials of dasatinib plus hormone therapy (HT) in advanced ER+ breast cancer (ER+ ABC) [ASCO abstract TPS133]. *J Clin Oncol.* 2010;28(15 suppl).
10. Awada A, Kaufman PA, Yelle L, et al. A phase III, open-label, randomized study of eribulin versus capecitabine in patients with metastatic breast cancer: effect of post-progression anti-cancer treatments and metastatic progression events on overall survival. Poster presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX. Abstract P3-13-03.
11. Kaufman PA, Awada A, Twelves C, et al. 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 [SABCS abstract S6-6]. *Cancer Res.* 2012;72(suppl 3). Abstract S6-6.
12. Mackey JR, Ramos-Vazquez M, Lipatov O, et al. Primary results of ROSE/TRIO-12, a randomized placebo controlled phase III trial evaluating the addition of ramucirumab to first-line docetaxel chemotherapy in metastatic breast cancer. Paper presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX. Abstract S5-04.
13. Mackey J, Gelmon K, Martin M, et al. TRIO-012: a multicenter, multinational, randomized, double-blind phase III study of IMC-1121B plus docetaxel versus placebo plus docetaxel in previously untreated patients with HER2-negative, unresectable, locally recurrent or metastatic breast cancer. *Clin Breast Cancer.* 2009;9(4):258-261.
14. McIntyre K, O'Shaughnessy J, Schwartzberg L, et al. Eribulin mesylate as first-line therapy for locally recurrent or metastatic HER2-negative breast cancer: results of a phase 2, multicenter, single-arm study. Poster presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX. Abstract P3-13-05.
15. Awada A, Spector N, El-Hariry I, et al. The ENCHANT-1 trial (NCT01677455): an open label multicenter phase 2 proof of concept study evaluating first line ganetespib monotherapy in women with metastatic HER2 positive or triple negative breast cancer (TNBC). Poster presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX. Abstract P2-16-23.
16. Wilks S, Puhalla S, O'Shaughnessy J, et al. Phase 2, multicenter, single-arm study of eribulin mesylate + trastuzumab as first-line therapy for locally recurrent or metastatic HER2-positive breast cancer. Poster presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX. Abstract P4-12-12.
17. Smerage JB, Barlow WE, Hayes DF, et al. SWOG S0500—a randomized phase III trial to test the strategy of changing therapy versus maintaining therapy for metastatic breast cancer patients who have elevated circulating tumor cell (CTC) levels at first follow-up assessment. Paper presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX. Abstract S5-07.
18. Cristofanilli M, Budd GT, Ellis MJ, et al. Circulating tumor cells, disease progression, and survival in metastatic breast cancer. *N Engl J Med.* 2004;351(8):781-791.
19. Hayes DF, Cristofanilli M, Budd GT, et al. Circulating tumor cells at each follow-up time point during therapy of metastatic breast cancer patients predict progression-free and overall survival. *Clin Cancer Res.* 2006;12(14, pt 1):4218-4224.
20. Liu MC, Shields PG, Warren RD, et al. Circulating tumor cells: a useful predictor of treatment efficacy in metastatic breast cancer. *J Clin Oncol.* 2009;27(31):5153-5159.
21. Kaufman PA, Yelle L, Cortes J, et al. Effect of age on tolerability and efficacy of eribulin and capecitabine in patients with metastatic breast cancer treated in study 301. Poster presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX. Abstract P3-13-04.
22. Dieras V, Yardley D, Romieu G, et al. A randomized, phase II, multicenter, double-blind, placebo-controlled trial evaluating onartuzumab with or without bevacizumab in combination with weekly paclitaxel in locally recurrent or metastatic triple-negative breast cancer (TNBC). Poster presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX. Abstract P2-16-01.
23. Luyimbazi D, Luu T, Xing Q, et al. Combination of eribulin and PI3K inhibitors in triple negative and HER2 expressing breast cancer cell lines results in synergistic growth inhibition and enhanced inhibition of the PI3K pathway. Poster presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX. Abstract P3-03-07.
24. Luyimbazi D, Luu T, Xing Q, et al. A comparison of PI3K inhibition by eribulin, other microtubule targeting agents and a DNA-damaging chemotherapeutic in triple negative and HER2 expressing breast cancer cell lines. Poster presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX. Abstract P3-03-08.
25. O'Shaughnessy JA, Gatalica Z, Kimbrough JM, Millis SZ. Comparison of mutations and protein expression in potentially actionable targets in 5500 triple negative vs. non-triple negative breast cancers. Poster presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX. Abstract PD4-1.
26. Smith BD, Leary CB, Kaufman MD, et al. Rebastinib in combination with eribulin ablates TIE2-expressing macrophages, reduces metastasis, and increases survival in the PyMT metastatic breast cancer model. Poster presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX. Abstract P4-15-12.
27. Iggo RD, Wood HM, Rabbitts P, et al. Next generation sequencing shows clonal selection after treatment with anastrozole or fulvestrant in a randomized

trial of postmenopausal patients with large operable or locally-advanced hormone-receptor-positive breast cancer. Poster presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX. Abstract PD3-3.
28. ClinicalTrials.gov. Anastrozole or fulvestrant in treating postmenopausal patients with breast cancer. http://clinicaltrials.gov/ct2/show/NCT00871858. Identifier: NCT00871858. Accessed February 18, 2014.
29. Serra V, Gris-Oliver A, Saura C, et al. PI3K blockade enhances the antitumor activity of eribulin in *PIK3CA*-mutant eribulin-resistant tumor xenografts. Poster presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX. Abstract P5-08-06.
30. Krop I, Lin N, Blackwell K, et al. Efficacy and safety of trastuzumab emtansine (T-DM1) vs lapatinib plus capecitabine (XL) in patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (MBC) and central nervous system (CNS) metastases: results from a retrospective exploratory analysis of EMILIA. Poster presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX. Abstract P4-12-27.
31. Verma S, Miles D, Gianni L, et al; for the EMILIA Study Group. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med.* 2012;367(19):1783-1791.
32. Blackwell KL, Hamilton EP, Marcom PK, et al. Exome sequencing reveals clinically actionable mutations in the pathogenesis and metastasis of triple negative breast cancer. Paper presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX. Abstract S4-03.
33. Robinson DR, Wu YM, Vats P, et al. Activating ESR1 mutations in hormone-resistant metastatic breast cancer. *Nat Genet.* 2013;45(12):1446-1451.
34. Toy W, Shen Y, Won H, et al. ESR1 ligand-binding domain mutations in hormone-resistant breast cancer. *Nat Genet.* 2013;45(12):1439-1445.
35. Hamilton E, Kimmick G, Hopkins J, et al. Nab-paclitaxel/bevacizumab/carboplatin chemotherapy in first-line triple negative metastatic breast cancer. *Clin Breast Cancer.* 2013;13(6):416-420.
36. Shah SP, Roth A, Goya R, et al. The clonal and mutational evolution spectrum of primary triple-negative breast cancers. *Nature.* 2012;486(7403):395-399.
37. Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. *Nature.* 2012;490(7418):61-70.

Commentary

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Many presentations at the 2013 San Antonio Breast Cancer Symposium (SABCS) provided new information to advance our understanding of the biology of metastatic breast cancer. Results from key clinical trials and diagnostic studies were presented.

Key Clinical Trial Results

Dr Devchand Paul from the US Oncology Network presented a study in patients with metastatic estrogen receptor (ER)-positive breast cancer that compared first-line treatment with letrozole alone vs letrozole plus dasatinib, an oral Src inhibitor.[1] The goal was to determine whether inhibition of Src could overcome resistance (emerging or de novo) to letrozole. Most of the patients in the study were de novo metastatic breast cancer patients and had not received previous treatment with endocrine therapy. The primary endpoint, clinical benefit rate, was high with both letrozole alone and letrozole plus dasatinib (66% vs 71%, respectively). The combination regimen improved progression-free survival from 9.9 months to 20 months, an interesting outcome suggesting that further studies examining Src inhibition in the first-line metastatic setting would be of interest. Dasatinib has been studied in the second-line setting.[2,3] Those trials did not show a benefit when dasatinib was added to second-line endocrine therapy (fulvestrant or exemestane), suggesting that inhibiting Src in the first-line setting, particularly in patients who have endocrine therapy–sensitive disease, may prevent the emergence of resistance to endocrine therapy. By the time patients are treated with second-line endocrine therapy and have developed resistance, Src inhibition may not be effective. The study by Dr Paul suggests that Src inhibition may prevent the emergence of endocrine therapy resistance in patients whose breast cancer is sensitive to letrozole.

Dr John Mackey presented results from the ROSE (Ramucirumab Overall Survival Evaluation)/TRIO-12 (Translational Research in Oncology) trial, which compared docetaxel alone vs docetaxel plus ramucirumab, an antibody against the vascular endothelial growth factor (VEGF) receptor 2. The trial enrolled more than 1100 patients receiving first-line metastatic breast cancer therapy.[4] The addition of ramucirumab to docetaxel did not significantly improve progression-free survival, the primary endpoint. This outcome adds to the question of whether antiangiogenesis therapy is effective in metastatic breast cancer. A trial examining bevacizumab in first-line metastatic breast cancer is ongoing. MERiDiAN (Study to Evaluate the Efficacy and Safety of Bevacizumab, and Associated Biomarkers, in Combination With Paclitaxel Compared With Paclitaxel Plus Placebo as First-Line Treatment of Patients With HER2-Negative Metastatic Breast Cancer)[5] is a confirmatory study of the E2100 trial,[6] in which progression-free survival was nearly doubled with the addition of bevacizumab to paclitaxel. The MERiDiAN trial is examining paclitaxel with or without

bevacizumab in patients stratified based on serum VEGF levels. The trial has completed enrollment, and results are awaited. The AVADO (Avastin and Docetaxel) trial of docetaxel with or without bevacizumab did not show the same degree of benefit as was seen with paclitaxel and bevacizumab.[7] There may be a synergistic effect between paclitaxel and antiangiogenesis inhibitors, and the docetaxel/ramucirumab combination in the ROSE/TRIO-12 trial may not have exploited this potential interaction. Results of the MERiDiAN trial will determine whether there is a role for antiangiogenesis inhibitors as first-line treatment for metastatic breast cancer.

Dr Véronique Diéras and colleagues examined onartuzumab, an antibody against *c-MET* also known as *MetMAb,* in a randomized, phase 2, double-blind, placebo-controlled, 3-arm trial in patients with triple-negative breast cancer.[8] Patients were randomized to weekly paclitaxel and bevacizumab; the triplet of paclitaxel, bevacizumab, and onartuzumab; or paclitaxel plus onartuzumab. The weekly paclitaxel/bevacizumab combination was associated with a median progression-free survival of approximately 7.6 months, which was not improved by the addition of onartuzumab. This study did not support the hypothesis that inhibition of *c-MET* in the context of paclitaxel and anti-VEGF therapy in triple-negative breast cancer patients is of therapeutic benefit. Most of the patients in this study had a *c-MET* immunohistochemistry (IHC) score of 0 or 1+, and few had substantial overexpression of c-MET. Many triple-negative breast cancers overexpress epidermal growth factor receptor (EGFR) positivity, and, in lung cancer, there is evidence that *c-MET* overexpression can be a mechanism of resistance to anti-EGFR therapy. Onartuzumab in combination with an anti-EGFR agent, such as cetuximab, might be worthy of evaluation in triple-negative breast cancer.

The phase 2 ENCHANT-1 (An Open Label Multicenter Phase 2 Window of Opportunity Study Evaluating Ganetespib [STA-9090] Monotherapy in Women With Previously Untreated Metastatic HER2 Positive or Triple Negative Breast Cancer [TNBC]) trial evaluated a novel Hsp90 inhibitor, ganetespib, in patients with human epidermal growth factor receptor 2 (HER2)-positive or triple-negative breast cancer.[9] The data presented at the 2013 SABCS focused on the triple-negative breast cancer population.[10] Positron emission tomography/computed tomography (PET/CT) scans were evaluated as an early indicator of response to single-agent, first-line ganetespib. In most patients, ganetespib was associated with significant PET/CT improvements, and some patients achieved a partial response. These encouraging data suggest that Hsp90 inhibition may be of potential benefit in triple-negative breast cancer patients. Hsp90 inhibitors are chaperone proteins that bind to nascent, newly formed proteins, allowing the proteins to fold into the correct conformations. By inhibiting Hsp90, toxic unfolded proteins accumulate within the cell, causing cytotoxicity. The Hsp90 inhibition strategy is a multitargeted approach to cancer cell inhibition, as the client proteins of the Hsp90 inhibitors are myriad, including several proteins in the phosphoinositide 3-kinase (PI3K) and MAP kinase pathways. Targeting Hsp90 is a promising pleiotropic approach to inhibition of triple-negative breast cancer.

Dr Ian Krop analyzed rates of central nervous system metastases with the EMILIA (An Open-Label Study of Trastuzumab Emtansine [T-DM1] vs Capecitabine Plus Lapatinib in Patients With HER2-Positive Locally Advanced or Metastatic Breast Cancer) trial, which compared trastuzumab emtansine (T-DM1) vs lapatinib plus capecitabine.[11,12] The subanalysis found no difference in the development of new brain metastases, the incidence of which was very low in this study. Among the patients who entered the trial with a history of brain metastases, there was substantial improvement in overall survival with T-DM1 compared with capecitabine plus lapatinib that mirrored the overall study results. This finding suggests that T-DM1 should be prospectively evaluated as a treatment for patients with HER2-positive brain metastases.

These were two phase 2 trials from the US Oncology Network examining the effectiveness of the novel microtubule inhibitor eribulin mesylate as first-line treatment for metastatic breast cancer. Dr Kristi McIntyre examined single-agent eribulin as first-line treatment for locally recurrent or metastatic HER2-negative breast cancer.[13] Dr Sharon Wilks presented results from a study of first-line eribulin plus trastuzumab in patients with locally recurrent or metastatic HER2-positive breast cancer.[14] Both studies showed very robust levels of antitumor activity. The combination of trastuzumab and eribulin was as active as any other single agent in this setting, and this regimen is now well-supported as an evidence-based option for patients with HER2-positive metastatic breast cancer. For patients whose disease has been pretreated with pertuzumab and T-DM1, eribulin plus trastuzumab is a reasonable option based on the safety and efficacy observed in this first-line trial. In the HER2-negative study, first-line, single-agent eribulin therapy demonstrated an objective response rate of 29%, a value similar to most other active agents in this setting, such as capecitabine.[15] Eribulin could be considered as an option for first-line treatment of metastatic breast cancer in patients who received an anthracycline and a taxane in the adjuvant setting and then developed rapid recurrence.

Study 301 compared eribulin and capecitabine in patients with locally advanced or metastatic breast cancer, and the results demonstrated no difference in progression-free survival, and a trend toward an improvement in

overall survival with eribulin.[16] A similar finding was shown in the EMBRACE (Eisai Metastatic Breast Cancer Study) trial, which compared eribulin to a treatment of the physician's choice as third-line or later-line therapy.[17] An analysis by Dr Ahmad Awada aimed to understand the lack of concordance between OS and PFS outcomes in Study 301.[18] This analysis examined whether therapies that patients received after treatment with eribulin or capecitabine affected overall survival. Dr Awada's analysis found no evidence that treatment with capecitabine or any other postprogression therapy accounted for the trend in improved overall survival observed with eribulin. Dr Awada and colleagues also attempted to better understand the improvement in survival with eribulin, by evaluating survival when progression occurred in existing metastases vs in new metastases that developed during treatment with eribulin or capecitabine. In patients who developed new metastases, there was an improvement in overall survival in favor of eribulin. When disease progressed in a pre-existing metastasis, there was no difference in survival in eribulin- and capecitabine-treated patients. In the capecitabine arm, more patients developed new visceral metastases, whereas with eribulin, there were fewer patients with new visceral metastases, and new metastases were more likely to be in nonvisceral sites, which are less likely to negatively impact overall survival. Dr Awada's interesting analysis is hypothesis-generating, and these findings should be evaluated in other phase 3 studies of eribulin.

In another analysis of Study 301,[16] Dr Peter Kaufman evaluated whether patients older than 65 years developed more toxicity than patients ages 65 years and younger receiving cytotoxic therapies.[19] In the capecitabine arm, patients who were older than 65 years experienced considerably more toxicity than patients younger than 65 years. In contrast, in the eribulin arm, toxicity was not substantially increased among the older patients. The adverse events in the older patients receiving capecitabine included diarrhea, dose reductions, and the need to stop therapy. This analysis suggests that older patients can begin therapy with eribulin at the standard dosage of 1.4 mg/m^2 on days 1 and 8. Dose reductions are generally not required in older patients when they begin treatment, allowing them to safely achieve the benefits of eribulin therapy.

An interesting phase 2 study presented by Dr Sara Giordano combined eribulin and carboplatin as preoperative therapy in triple-negative breast cancer patients.[20] In a separate study from the Cancer and Leukemia Group B presented by Dr William Sikov, the addition of carboplatin to standard preoperative chemotherapy improved the pathologic complete response rate in triple-negative breast cancer patients.[21] The study by Dr Giordano demonstrated that it is possible to administer full-dose carboplatin (area under the curve of 6) with full-dose eribulin; the pathologic complete response rate with the combination was approximately 46%. The results of this study suggest that this combination should be evaluated in a larger cohort of locally advanced triple-negative breast cancer patients. In Study 301, eribulin was associated with improved survival in triple-negative breast cancers (14 months with eribulin vs 9 months with capecitabine), demonstrating that eribulin is an important agent in the treatment of triple-negative breast cancer.[16] It would be of interest to compare eribulin with taxane-based therapy as neoadjuvant treatment for triple-negative disease.

The Southwest Oncology Group (SWOG) S0500 study examined the clinical utility of circulating tumor cells (CTCs) in patients receiving first-line treatment for metastatic breast cancer.[22] Enrolled patients had at least 5 CTCs per 7.5 mL of whole blood, and following cycle 1 of their first-line chemotherapy of physician's choice, they underwent repeat assessment of CTCs. Patients who had persistently elevated CTCs of 5 or higher were randomly assigned to continue the same chemotherapy or to switch to a different chemotherapy of the physician's choice. It was postulated that switching chemotherapy at the time of persistently elevated CTCs may improve overall survival, the primary endpoint. The results of this study demonstrated that the switch to a different cytotoxic agent did not improve progression-free survival or overall survival compared with continued treatment on the initial chemotherapy. It was clear, however, that patients with persistently elevated CTCs had a poorer overall survival outcome than patients whose CTCs decreased to less than 5 with therapy. This study reiterated the known importance of CTC levels as a prognostic factor in metastatic breast cancer. It also highlighted the fact that patients who have persistently elevated CTCs after a first cycle of chemotherapy for metastatic breast cancer have a poor prognosis. These patients may be best served by enrolling in clinical trials aimed at developing novel targeted therapies to overcome chemotherapy resistance.

Studies Revealing Novel Biologic Insights

A series of preclinical studies examined eribulin mesylate in the context of PI3K signaling. PI3K signaling is an important mechanism of resistance and survival in triple-negative breast cancers[23] and some aggressive ER-positive breast cancers.[24] Two preclinical studies presented by Dr David Luyimbazi examined triple-negative and HER2-positive breast cancer cell lines and showed that in the setting of PI3K mutations or PTEN loss, there was highly synergistic activity between eribulin and inhibitors of the PI3K pathway, such as BKM120 (buparlisib) and BYL719, an α-specific PI3K inhibitor.[25,26]

The first study showed synergy with eribulin plus PI3K inhibitors in triple-negative breast cancers.[25] This finding

is of high interest because single-agent eribulin has been shown to improve progression-free and overall survival in metastatic triple-negative breast cancer patients. In Study 301, eribulin was compared with capecitabine as second-line treatment of metastatic breast cancer patients who had received previous treatment with a taxane.[16] Among the entire population, there was a trend toward improvement in overall survival with eribulin, but no difference in progression-free survival. Among the patients with triple-negative breast cancer, however, eribulin improved progression-free survival and overall survival. Triple-negative breast cancers are known to have activated the PI3K signaling pathway,[23] and this may contribute to their resistance to many chemotherapy agents.[27] Clinical trials of eribulin, with or without PI3K inhibitors, would be of considerable interest, particularly in the triple-negative breast cancer population.

The other study by Luyimbazi and colleagues compared eribulin vs vinblastine, a vinca alkaloid that inhibits microtubule polymerization, vs paclitaxel as well as the DNA-damaging agent cisplatin in the context of PI3K pathway activation.[26] Eribulin and vinblastine, agents that prevent microtubule polymerization, inhibited triple-negative breast cancer cells that had *PIK3CA* mutations or PTEN loss. Paclitaxel and cisplatin did not inhibit triple-negative or HER2-expressing breast cancer cell lines with PI3K pathway activation. These interesting observations suggest that there are differences among cytotoxic agents in their ability to inhibit breast cancer cells that have activation of the PI3K pathway. This theory is supported by clinical trials, such as Study 301, in which pretreated triple-negative metastatic breast cancer patients experienced improved overall survival with eribulin compared with capecitabine.[16] The PI3K pathway has been shown to be activated in primary triple-negative breast cancers in the Cancer Genome Atlas evaluation of protein phosphorylation in the PI3K pathway.[28] The ongoing clinical trials of paclitaxel with or without the PI3K inhibitors buparlisib and GDC-0941 will provide insights into PI3K pathway inhibition in metastatic triple-negative breast cancer.[29,30]

Dr Violeta Serra studied eribulin and PI3K blockade in vitro, using a panel of HER2-negative breast cancer cell lines, and in vivo, using xenografts derived from cell lines or directly from patients.[31] Some of the tumor models showed resistance to eribulin, which was overcome by the inhibition of the PI3K pathway. This finding is important as it extends our knowledge beyond cell lines into murine tumor xenografts and patient-derived xenografts, and shows synergistic antitumor activity with combined eribulin and PI3K pathway blockade. These data provide additional support for exploring eribulin and PI3K pathway inhibitors in the clinical setting, especially in pretreated patients with taxane-resistance, where PI3K pathway activation may be of particular importance.

Dr Bryan Smith presented an interesting preclinical evaluation of eribulin in combination with rebastinib, a Tie2 kinase inhibitor that is expressed on macrophages, vascular endothelial cells, and monocytes.[32] This regimen led to the ablation of the macrophages that infiltrate breast cancers and cause invasion and metastasis. This combination decreased lung metastases and improved overall survival in animal models. Dr Hope Rugo is leading a clinical trial combining eribulin with a colony-stimulating factor-1 inhibitor, which is also directed against tumor-infiltrating macrophages.[33] Testing these combinations in metastatic breast cancer patients will determine whether ablation of macrophages in the tumor microenvironment leads to improved treatment outcomes in combination with eribulin.

I presented results from a study examining archival tissues from 5500 patients with metastatic or high-risk breast cancer to identify the key actionable mutations in triple-negative and non–triple-negative disease.[34] The key finding was that androgen receptor expression is present in 18% of triple-negative breast cancers, 50% of ER-negative/HER2-positive cancers, and the majority of ER-positive breast cancers. The archival tissues studied were from a commercial laboratory that performs a multiplatform assessment of potentially targetable mutations in metastatic disease. Our analysis showed a strong concordance between the incidence of mutations in primary and metastatic breast cancer tissues. The androgen receptor–positive breast cancers nearly always had a detectable genomic alteration that could lead to activation of the PI3K pathway, including PIK3CA and/or PTEN mutations or PTEN loss by IHC. There appears to be coactivation of the androgen receptor and the PI3K pathway in a subset of triple-negative breast cancers and also in HER2-positive, androgen receptor–positive breast cancers. Androgen receptor–positive, triple-negative breast cancers tended to have a lower proliferative rate assessed by central laboratory analysis, whereas androgen receptor–negative, triple-negative breast cancers were generally very highly proliferative. Interestingly, amplification of the *EGFR* gene was found in 20% of triple-negative breast cancers. The study identified several potentially targetable mutations that should be prospectively evaluated in clinical trials, including the combination of an androgen receptor and PI3K pathway inhibitors in ER-negative, androgen receptor–positive breast cancer.

A study by Dr Richard Iggo examined preoperative anastrozole vs fulvestrant in postmenopausal patients with locally advanced, ER-positive breast cancer.[35] Overall, approximately three-quarters of patients' cancers demonstrated a substantial reduction in proliferation assessed on Ki-67 analysis. The response rate was somewhat higher with anastrozole than with the fulvestrant dosage of 500 mg monthly. Next-generation sequencing that compared the

upfront original biopsy of the cancer with a biopsy of the residual cancer obtained after 6 months of on-study treatment identified clonal selection. The residual disease had a higher incidence of genomic alterations in the ER signaling pathway, including amplicons of the *ESR1*, *FOXA1*, and *NCOA3* genes. This study showed that antiestrogen therapy with anastrozole and fulvestrant was effective in eradicating or inhibiting breast cancer cells in the preoperative setting and led to clonal selection of residual disease that had abnormalities in the ER-signaling pathway. This finding is particularly interesting when considered in light of a study by Dr Zhi-Ming Shao, which showed that up to approximately 30% of ER-positive metastatic breast cancers have a mutation in the ER gene that leads to constitutive activation of the ER.[36] This finding raises the question of whether these ER mutations, which are rarely seen in primary breast cancers, are acquired owing to selective pressure of antiestrogen therapies, leading to the emergence of resistance via an activated ER mutation. Or, are ER-mutated subclones in primary breast cancers present at a very low frequency and does clonal selection occur during anti–ER-directed therapy? In this way, the antiestrogen therapies lead to substantial cytoreduction of most of the ER-positive breast cancer cells, leaving behind a resistant subclone of ER-mutated breast cancers. There is ongoing debate regarding whether the findings of ER-mutated metastatic breast cancer represent clonal evolution (ie, the development of acquired, new mutations) or clonal selection (ie, an outgrowth of a rare population). Dr Suzanne Fuqua presented data suggesting that clonal outgrowth of rare populations that are preexisting in the primary breast cancers can occur.[37] The study by Dr Iggo also suggests that clonal selection with preoperative anastrozole/fulvestrant occurs with residual disease containing amplicons in genes in the ER pathway. The possibility of acquired mutations in the ER raise questions about the safety of indefinite duration of endocrine therapy in the adjuvant setting. Developing inhibitors of mutant ER has become a high priority, as has understanding whether existing standard therapies are effective against this new subtype of ER-positive metastatic breast cancer.

Acknowledgment

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References

1. Paul D, Vukelja SJ, Holmes FA, et al. Letrozole plus dasatinib improves progression-free survival (PFS) in hormone receptor-positive, HER2-negative postmenopausal metastatic breast cancer (MBC) patients receiving first-line aromatase inhibitor (AI) therapy. Paper presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX. Abstract S3-07.

2. Wright GL, Blum J, Krekow LK, et al. Randomized phase II trial of fulvestrant with or without dasatinib in postmenopausal patients with hormone receptor-positive metastatic breast cancer previously treated with an aromatase inhibitor [SABCS abstract PD01-01]. *Cancer Res*. 2011;71(24 suppl).

3. Mayer EL, Baurain JF, Sparano J, et al. A phase 2 trial of dasatinib in patients with advanced HER2-positive and/or hormone receptor-positive breast cancer. *Clin Cancer Res*. 2011;17(21):6897-6904.

4. Mackey JR, Ramos-Vazquez M, Lipatov O, et al. Primary results of ROSE/TRIO-12, a randomized placebo controlled phase III trial evaluating the addition of ramucirumab to first-line docetaxel chemotherapy in metastatic breast cancer. Paper presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX. Abstract S5-04.

5. Miles D, Faoro L, Wang YV, et al. MERiDiAN: a phase III, randomized, double-blind study of the efficacy, safety, and associated biomarkers of bevacizumab plus paclitaxel compared with paclitaxel plus placebo, as first-line treatment of patients with HER2-negative metastatic breast cancer [ASCO abstract TPS1142^]. *J Clin Oncol*. 2013;31(15 suppl).

6. Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med*. 2007;357(26):2666-2676.

7. Pivot X, Schneeweiss A, Verma S, et al. Efficacy and safety of bevacizumab in combination with docetaxel for the first-line treatment of elderly patients with locally recurrent or metastatic breast cancer: results from AVADO. *Eur J Cancer*. 2011;47(16):2387-2395.

8. Diéras V, Yardley D, Romieu G, et al. A randomized, phase II, multicenter, double-blind, placebo-controlled trial evaluating onartuzumab with or without bevacizumab in combination with weekly paclitaxel in locally recurrent or metastatic triple-negative breast cancer (TNBC). Poster presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX. Abstract P2-16-01.

9. Awada A, Rodriguez AA, Kong A, et al. The ENCHANT-1 trial (NCT01677455): an open label multicenter phase II proof of concept study evaluating first-line ganetespib monotherapy in women with metastatic HER2-positive or triple-negative breast cancer (TNBC) [ASCO abstract TPS1136]. *J Clin Oncol*. 2013;31(15 suppl).

10. Awada A, Spector N, El-Hariry I, et al. The ENCHANT-1 trial (NCT01677455): an open label multicenter phase 2 proof of concept study evaluating first line ganetespib monotherapy in women with metastatic HER2 positive or triple negative breast cancer (TNBC). Poster presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX. Abstract P2-16-23.

11. Krop I, Lin N, Blackwell K, et al. Efficacy and safety of trastuzumab emtansine (T-DM1) vs lapatinib plus capecitabine (XL) in patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (MBC) and central nervous system (CNS) metastases: results from a retrospective exploratory analysis of EMILIA. Poster presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX. Abstract P4-12-27.

12. Verma S, Miles D, Gianni L, et al; for the EMILIA Study Group. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med*. 2012;367(19):1783-1791.

13. McIntyre K, O'Shaughnessy J, Schwartzberg L, et al. Eribulin mesylate as first-line therapy for locally recurrent or metastatic HER2-negative breast cancer: results of a phase 2, multicenter, single-arm study. Poster presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX. Abstract P3-13-05.

14. Wilks S, Puhalla S, O'Shaughnessy J, et al. Phase 2, multicenter, single-arm study of eribulin mesylate + trastuzumab as first-line therapy for locally recurrent or metastatic HER2-positive breast cancer. Poster presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX. Abstract P4-12-12.

15. Gilabert M, Bertucci F, Esterni B, et al. Capecitabine after anthracycline and taxane exposure in HER2-negative metastatic breast cancer patients: response, survival and prognostic factors. *Anticancer Res*. 2011;31(3):1079-1086.

16. Kaufman PA, Awada A, Twelves C, et al. 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 [SABCS abstract S6-6]. *Cancer Res*. 2012;72(suppl 3).

17. Cortes J, O'Shaughnessy J, Loesch D, et al; EMBRACE (Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389) investigators. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomized study. *Lancet*. 2011;377(9769):914-923.

18. Awada A, Kaufman PA, Yelle L, et al. A phase III, open-label, randomized study of eribulin versus capecitabine in patients with metastatic breast cancer: effect of post-progression anti-cancer treatments and metastatic progression events on overall survival. Poster presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX. Abstract P3-13-03.

19. Kaufman PA, Yelle L, Cortes J, et al. Effect of age on tolerability and efficacy of eribulin and capecitabine in patients with metastatic breast cancer treated in study 301. Poster presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX. Abstract P3-13-04.

20. Giordano SB, Jeruss JS, Bethke KP, et al. Neoadjuvant phase II trial with carboplatin and eribulin in triple negative breast cancer patients. Poster presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX. Abstract P3-14-14.
21. Sikov WM, Berry DA, Perou CM, et al. S5-01: impact of the addition of carboplatin (Cb) and/or bevacizumab (B) to neoadjuvant weekly paclitaxel (P) followed by dose-dense AC on pathologic complete response (pCR) rates in triple-negative breast cancer (TNBC): CALGB 40603 (Alliance). Poster presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX. Abstract S5-01.
22. Smerage JB, Barlow WE, Hayes DF, et al. S0500—a randomized phase III trial to test the strategy of changing therapy versus maintaining therapy for metastatic breast cancer patients who have elevated circulating tumor cell (CTC) levels at first follow-up assessment. Paper presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX. Abstract S5-07.
23. Gordon V, Banerji S. Molecular pathways: PI3K pathway targets in triple-negative breast cancers. *Clin Cancer Res*. 2013;19(14):3738-3744.
24. Miller TW, Hennessy BT, González-Angulo AM, et al. Hyperactivation of phosphatidylinositol-3 kinase promotes escape from hormone dependence in estrogen receptor-positive human breast cancer. *J Clin Invest*. 2010;120(7):2406-2413.
25. Luyimbazi D, Luu T, Xing Q, et al. Combination of eribulin and PI3K inhibitors in triple negative and HER2 expressing breast cancer cell lines results in synergistic growth inhibition and enhanced inhibition of the PI3K pathway. Poster presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX. Abstract P3-03-07.
26. Luyimbazi D, Luu T, Xing Q, et al. A comparison of PI3K inhibition by eribulin, other microtubule targeting agents and a DNA-damaging chemotherapeutic in triple negative and HER2 expressing breast cancer cell lines. Poster presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX. Abstract P3-03-08.
27. André F, Zielinski CC. Optimal strategies for the treatment of metastatic triple-negative breast cancer with currently approved agents. *Ann Oncol*. 2012;23(suppl 6):vi46-vi51.
28. Cancer Genome Atlas Research Network, Weinstein JN, Collisson EA, et al. The Cancer Genome Atlas Pan-Cancer analysis project. *Nat Genet*. 2013;45(10):1113-1120.
29. ClinicalTrials.gov. A study of the experimental drug BKM120 with paclitaxel in patients with HER2 negative, locally advanced or metastatic breast cancer, with or without PI3K activation (BELLE-4). http://clinicaltrials.gov/ct2/show/NCT01572727. Identifier: NCT01572727. Accessed February 12, 2014.
30. ClinicalTrials.gov. A study of paclitaxel with GDC-0941 versus paclitaxel with placebo in patients with locally recurrent or metastatic breast cancer. http://clinicaltrials.gov/ct2/show/NCT01740336. Identifier: NCT01740336. Accessed February 12, 2014.
31. Serra V, Gris-Oliver A, Saura C, et al. PI3K blockade enhances the antitumor activity of eribulin in PIK3CA-mutant eribulin-resistant tumor xenografts. Poster presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX. Abstract P5-08-06.
32. Smith BD, Leary CB, Kaufman MD, et al. Rebastinib in combination with eribulin ablates TIE2-expressing macrophages, reduces metastasis, and increases survival in the PyMT metastatic breast cancer model. Poster presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX. Abstract P4-15-12.
33. ClinicalTrials.gov. Phase Ib/II study of PLX 3397 and eribulin in patients with metastatic breast cancer. http://clinicaltrials.gov/ct2/show/NCT01596751. Identifier: NCT01596751. Accessed February 12, 2014.
34. O'Shaughnessy JA, Gatalica Z, Kimbrough JM, Millis SZ. Comparison of mutations and protein expression in potentially actionable targets in 5500 triple negative vs. non-triple negative breast cancers. Poster presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX. Abstract PD4-1.
35. Iggo RD, Wood HM, Rabbitts P, et al. Next generation sequencing shows clonal selection after treatment with anastrozole or fulvestrant in a randomized trial of postmenopausal patients with large operable or locally-advanced hormone-receptor-positive breast cancer. Poster presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX. Abstract PD3-3.
36. Shao J, Li S, Crowder RJ, et al. Patient-derived xenograft study reveals endocrine therapy resistance of ER+ breast cancer caused by distinct ESR1 gene aberrations. Poster presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX. Abstract S3-05.
37. Furqua SAW. Basic Science 101: understanding nuclear receptors in breast cancer. Paper presented at: 2013 San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX. Session ES04.

Highlights in Metastatic Breast Cancer From the 2013 San Antonio Breast Cancer Symposium

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

1. What was the clinical benefit rate of letrozole plus dasatinib in a phase 2 trial of hormone receptor–positive, HER2-negative postmenopausal metastatic breast cancer patients receiving first-line aromatase inhibitor therapy?

a. 43%
b. 57%
c. 68%
d. 71%

2. In the ROSE/TRIO-12 trial, what was the median investigator-assessed PFS with ramucirumab plus docetaxel?

a. 6.8 months
b. 7.1 months
c. 9.5 months
d. 10.3 months

3. In a phase 2 trial of eribulin mesylate as first-line therapy for locally recurrent or metastatic HER2-negative breast cancer, what was the overall objective response rate?

a. 24.8%
b. 28.6%
c. 32.1%
d. 35.6%

4. In a phase 2 trial evaluating onartuzumab with or without bevacizumab in combination with weekly paclitaxel in locally recurrent or metastatic triple-negative breast cancer, which regimen was associated with the longest median overall survival?

a. Paclitaxel and bevacizumab
b. Paclitaxel, bevacizumab, and onartuzumab
c. Paclitaxel and onartuzumab
d. There was no significant difference

5. In a trial testing the strategies of changing chemotherapy vs maintaining therapy in patients with elevated circulating tumor cells, which approach was associated with increased progression-free survival?

a. Changing chemotherapy
b. Maintaining therapy
c. There was no significant difference

6. Which agent is a second-generation inhibitor of heat shock protein 90?

a. Ganetespib
b. Ramucirumab
c. Rebastinib
d. Vincristine

7. In a comparison of mutations and protein expression in potentially actionable targets in triple-negative vs non–triple-negative breast cancers, the androgen receptor was expressed in ___ of cancers that were ER-negative.

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

8. Which pathway is targeted by onartuzumab?

a. Angiopoietin/TIE2
b. MET
c. Phosphoinositide 3-kinase
d. Vascular endothelial growth factor

9. Which gene is not involved in estrogen signaling?

a. *ESR1*
b. *FOXA1*
c. *LAMA3*
d. *NCOA3*

10. In an analysis of patients with central nervous system metastases in the EMILIA trial, which treatment was associated with a higher overall survival?

a. Capecitabine
b. Trastuzumab emtansine
c. There was no significant difference

Project ID: 9826

Evaluation Form: Highlights in Metastatic Breast Cancer From the 2013 San Antonio Breast Cancer Symposium

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 9826**. Upon successfully registering/logging in, completing the post-test and evaluation, your certificate will be made available immediately.

1. What degree best describes you?

❒ MD/DO ❒ PA/PA-C ❒ NP ❒ RN ❒ PharmD/RPh ❒ PhD
❒ Other, please specify:

2. What is your area of specialization?

❒ Oncology, Hematology/Oncology ❒ Oncology, Medical ❒ Oncology, Other

3. Which of the following best describes your *primary* practice setting?

❒ Solo Practice ❒ Group Practice ❒ Government
❒ University/teaching system ❒ Community Hospital
❒ HMO/managed care ❒ Non-profit/community ❒ I do not actively practice
❒ Other, please specify:

4. How long have you been practicing medicine?

❒ More than 20 years ❒ 11-20 years ❒ 5-10 years ❒ 1-5 years
❒ Less than 1 year ❒ I do not directly provide care

5. Approximately how many patients do you see each week?

❒ Less than 50 ❒ 50-99 ❒ 100-149 ❒ 150-199 ❒ 200+
❒ I do not directly provide care

6. How many patients do you currently see each week with breast cancer?

❒ Fewer than 5 ❒ 6-15 ❒ 16-25 ❒ 26-35 ❒ 36-45 ❒ 46-55
❒ 56 or more ❒ I do not directly provide care

7. Rate how well the activity supported your achievement of these learning objectives:

Evaluate efficacy and safety data for new and emerging agents for the treatment of metastatic breast cancer

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Incorporate newly approved agents into treatment regimens to improve response and survival outcomes of metastatic breast cancer patients

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Implement individualized management plans based on factors such as hormone receptor and human epidermal growth factor receptor 2 status, previous therapies, tumor burden, patient age, and comorbidities

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Discuss future research directions and novel targets in the treatment of metastatic breast cancer

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

8. Rate how well the activity achieved the following:

The faculty were effective in presenting the material

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The content was evidence based

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The educational material provided useful information for my practice

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The activity enhanced my current knowledge base

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The activity provided appropriate and effective opportunities for active learning (e.g., case studies, discussion, Q&A, etc.)

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The opportunities provided to assess my own learning were appropriate (e.g., questions before, during or after the activity)

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

9. Based upon your participation in this activity, do you intend to change your practice behavior? *(choose only one of the following options)*

❒ I do plan to implement changes in my practice based on the information presented

❒ My current practice has been reinforced by the information presented

❒ I need more information before I will change my practice

10. Thinking about how your participation in this activity will influence your patient care, how many of your patients are likely to benefit?

Please use a number (for example, 250):

11. If you plan to change your practice behavior, what type of changes do you plan to implement? *(check all that apply)*

❒ Apply latest guidelines ❒ Choice of treatment/management approach
❒ Change in pharmaceutical therapy ❒ Change in current practice for referral
❒ Change in nonpharmaceutical therapy ❒ Change in differential diagnosis
❒ Change in diagnostic testing ❒ Other, please specify:

12. How confident are you that you will be able to make your intended changes?

❒ Very confident ❒ Somewhat confident ❒ Unsure ❒ Not very confident

13. Which of the following do you anticipate will be the primary barrier to implementing these changes?

❒ Formulary restrictions ❒ Insurance/financial issues ❒ Time constraints
❒ Lack of multidisciplinary support ❒ System constraints
❒ Treatment-related adverse events ❒ Patient adherence/compliance
❒ Other, please specify:

14. Was the content of this activity fair, balanced, objective and free of bias?

❒ Yes ❒ No, please explain:

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

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Telephone _____ Fax _____

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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 1.75 credits.
❒ I participated in only part of the activity and claim _____ credits.

Post-test Answer Key

1	2	3	4	5	6	7	8	9	10

Project ID: **9826**